SICKLE CELL DISEASE IN CHILDREN AND ADOLESCENTS: DIAGNOSIS, GUIDELINES FOR COMPREHENSIVE CARE, AND PROTOCOLS FOR MANAGEMENT OF ACUTE AND CHRONIC COMPLICATIONS©

Mid-Atlantic Sickle Cell Disease Consortium (MASCC) Practice Guidelines Workgroup sponsored by the Mid-Atlantic Regional Human Genetics Network (MARHGN)

This document represents a consensus with regard to standards of and expectations for comprehensive care for infants, children, and adolescents with sickle cell disease. Pediatric hematologists, nurses, and other health care professionals with expertise in the medical management of children with sickle cell disease from the Mid-Atlantic region representing Delaware, the District of Columbia, Maryland, New Jersey, Pennsylvania, Virginia, and West Virginia developed this set of guidelines. This group met several times from September 1998 through January 2001. These standards and expectations assume both the professional expertise and clinical facilities necessary to provide this level of care. It is strongly recommended that patients with sickle cell disease who are acutely ill be evaluated and treated at a comprehensive sickle cell disease center.

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Introduction

Significant progress has been made during the past 10–20 years in the treatment of sickle cell disease. Identification of most affected infants by neonatal screening provides opportunities for educational and medical interventions that significantly reduce morbidity and mortality during childhood and adolescence. Comprehensive medical care includes extensive health maintenance with appropriate prophylactic measures, parental education, psychosocial support, and periodic medical assessment with monitoring for the development of chronic organ dysfunction. Appropriate sickle cell disease care also provides for the management of acute illness in a setting where knowledge and perspective about sickle cell disease is available and where physicians have ready access to baseline information about the patient, including results of previous physical examinations, laboratory work, and radiographs. Because acute illness in patients with sickle cell disease can prove rapidly life threatening, it is essential that patients have unimpeded access to physicians who have the perspective necessary to quickly recognize and treat potentially catastrophic signs and symptoms. Such care not only reduces morbidity and mortality; it reduces overall medical costs by preventing some manifestations of the disease and by limiting the severity or sequelae of others. Many acute complications can be managed safely on an outpatient basis, reducing the need for hospitalization.

This manual provides information about the diagnosis of sickle cell disease, an overview of comprehensive care, and protocols for the management of some of the more common acute and chronic complications. *These protocols are intended to serve as general guidelines, and it is recognized that deviations from them will be appropriate in individual cases. It is also recognized that this manual addresses only the more common pediatric complications and should not be used as a substitute for hands-on care by providers with experience and expertise in the management of sickle cell disease.* Nevertheless, it is expected that adherence to these protocols will improve the consistency and quality of care, while at the same time minimizing costs by preventing some complications and by avoiding unnecessary laboratory tests, diagnostic procedures, and hospitalizations.

Newborn Screening Follow-Up Guidelines

Follow-Up Procedures for Infants with Probable Hemoglobin Disease
(Newborn screening results FS, FSC, FSA, FSVariant, FVariant, F only)

Newborn screening for sickle cell disease is the first step in a program to reduce the morbidity and mortality associated with this disease by identifying affected infants at birth, initiating prophylactic penicillin as soon as possible, and providing ongoing care by knowledgeable health professionals. This program is both necessary and effective. Early studies documented a high mortality rate in children with sickle cell disease during the first 5 years of life from infection and splenic sequestration (Diggs; Thomas et al.; Seeler). The reports of Powars et al. and others (Grover et al.; Pearson; John et al.) show that early diagnosis and comprehensive care can significantly reduce mortality and morbidity in children with sickle cell disease. The indisputable benefits of prophylaxis with penicillin in preventing *Streptococcus pneumoniae* septicemia were demonstrated in a blinded, randomized, controlled study and provided a firm scientific rationale for newborn screening (Gaston et al.). After this study was published, a National Institutes of Health Consensus Development Conference concluded that every child should be screened early in life for sickle cell disease to prevent death during infancy (see table 1).

Table 1
Conclusions of NIH Consensus Development Conference

1.	Prophylactic penicillin therapy provided in the setting of comprehensive care prevents morbidity and mortality.
2.	Reliable, simple, and cost-effective techniques with demonstrated validity are available for screening.
3.	Universal screening, mandated by state law, should be provided.
4.	Laboratory services should be centralized to improve efficiency and reduce probability of error.
5.	Neonatal screening must be a component of a comprehensive program that provides medical care, psychosocial support, and genetic counseling to patients and families. Screening should not be initiated until these services are in place.
6.	There is need for future research on testing technology, the impact of screening on patients and family, managing infectious complications, and educating individuals at risk.

Specific details concerning newborn screening programs vary from state to state. However, the general components of a newborn screening program are as follows:

1. **Collect a Sample**
   A sample is collected from all infants using dry blood spots on filter paper or liquid cord blood. According to the current standards of the National Committee for Clinical Laboratory Standards, initial testing methods must be of high sensitivity and reasonable specificity.

2. **Report Positive Screening Results**
   The newborn screening laboratory reports positive results indicating potential sickle cell disease or other hemoglobinopathy (FS, FSC, FSA, FSVariant, FVariant, F only) (see table 2) promptly to the hospital, sample submitter, and/or newborn screening program follow-up

coordinator (the recipients vary by state). The infant's primary care physician is also notified, *as well as the regional specialist.*

The goal is to contact families of identified infants *by 3 weeks of age.*

3. **Retrieve Infants with Positive Screening Results for Confirmatory Testing and Follow-Up**
Infants suspected of having sickle cell disease are retrieved for diagnostic evaluation, initiation of treatment, and parent education. The official retrieving infants varies by state; it might be the primary care provider, state newborn screening coordinator, or public health nurse. If the family declines any type of medical follow-up and all follow-up attempts have been unsuccessful and thoroughly documented, it is appropriate to notify child protective services.

The hospital, primary care physician, or regional specialist arranges for confirmatory testing in an appropriate laboratory familiar with performing and interpreting newborn hemoglobinopathy screening *by 2 months of age.*

The definitive diagnosis must be made after consulting with a pediatric hematologist. To establish the correct diagnosis with some infants, testing of parents, siblings, and other family members might be required. In some cases, definitive diagnosis might require other testing such as globin gene analysis or hemoglobin protein structural studies.

4. **Start Infants on Prophylactic Penicillin**

Infants with initial screening results suggesting sickle cell anemia should be started on oral penicillin prophylaxis (125mg PO BID) while the phenotype is being confirmed *by 2 months of age.*

5. **Arrange for Consultation, Education, and Genetic Counseling**

Consulting with a pediatric hematologist is essential to making a definitive diagnosis and should occur *by 2 months of age.*

A health professional knowledgeable about sickle cell disease (ideally a pediatric hematologist or staff member of a sickle cell clinic) provides the family with education and written information about the disorder and its treatment. Early education about sickle cell disease emphasizes the importance of prompt medical evaluation for fever and signs or symptoms of splenic sequestration. The medical center establishes a comprehensive, ongoing treatment and follow-up plan. The role of testing parents, siblings, and other family members is discussed. Genetic counseling is provided.

6. **Report Confirmatory Results**
Confirmatory results are reported to the family in an appropriate and sensitive manner. These results are also reported to the infant's primary care provider and newborn screening program

follow-up coordinator, as well as the screening laboratory (which varies by state) so it can monitor the performance of the laboratory and follow-up programs. When appropriate, results are also sent to the hospital of birth and to the state reports and records department for storage and program analysis. Ideally, results are linked to birth records to ensure that all infants are tested.

Carriers of hemoglobin variants may be identified in a similar manner (see Follow-Up Procedures for Infants with Probable Hemoglobinopathy Trait, below). At a minimum, the results must be communicated to the family, primary care provider, and hospital of birth or public health nurse caring for the infant. Family members of the affected infant identified as having a hemoglobinopathy trait should be offered testing, counseling, and education.

Table 2
Sickle Hemoglobinopathies: Diagnostic Test Results

Disorder	Hb Electrophoresis Pattern by 6 Weeks of Age[a]	Clinical Hematologic Features	Hematologic Studies by 2 Years				DNA Dot Blot		Parents' Usual Phenotypes[d]	
			MCV[b]	Hb A_2 (%)[c]	Hb F (%)	Hb F Distribution				
SCD-SS	FS	Hemolysis and anemia by 6–12 months	N or ↑[e]	< 3.6[e]	< 25	Heterocellular	β^S		AS	AS
SCD-Sβ^o-thal	FS	Hemolysis and anemia by 6–12 months	↓[e]	> 3.6[e]	< 25	Heterocellular	β^S		AS	A ↓MCV ↑A_2 N or ↑F
SCD-S$\delta\beta$-thal	FS	Mild anemia by 2 years	↓	< 2.5	< 25	Heterocellular	β^S		AS	AF ↓MCV ↑A_2, ↑F
S HPFH	FS	No hemolysis or anemia	N or ↓	< 2.5	< 25	Pancellular	β^S		AS	AF ↑F
SCD-S β+- thal	FSA	Mild or no anemia by 2 years	N or ↓	> 3.6	< 25	NA[f]	β^A	β^S	AS	A ↓MCV ↑A_2 N or ↑F
SCD-SC	FSC	Mild or no anemia by 2 years	N or ↓	NA[g]	< 15	NA[f]	β^S	β^C	AS	AC

Notes: Table shows typical results; exceptions occur. Some rare genotypes (for example, SD, SO^{Arab}, SC^{Harlem}, S Lepore, and SE) are not included. SCD = sickle cell disease, thal = thalassemia, N = Normal, ↑ = increased, ↓ = decreased.

[a]Hemoglobin is reported in order of quantity (for example, in FSA, F > S > A).

[b]Normal MCV is ≥ 70 at 6–12 months of age and ≥ 72 at 1–2 years of age.

[c]Hb A_2 results vary somewhat depending on laboratory methodology.

[d]Assumes the absence of uniparental disomy and that parents are heterozygous. In some cases parents might be homozygous or compound heterozygous.

[e]Hb SS with coexistent alpha thalassemia may cause decreased MCV and Hb A_2 > 3.6%. However, the newborn screening sample from these infants might show Hb Bart's.

[f]Not applicable; test not indicated.

[g]Not applicable; the quantity of Hb A_2 is usually not measured in the presence of Hb C.

Follow-Up Procedures for Infants with Probable Hemoglobinopathy Trait

Inclusive of newborn screening results FAS, FAC, FAE, FAU, FAV (other hemoglobin variant), exclusive of Hb Bart's

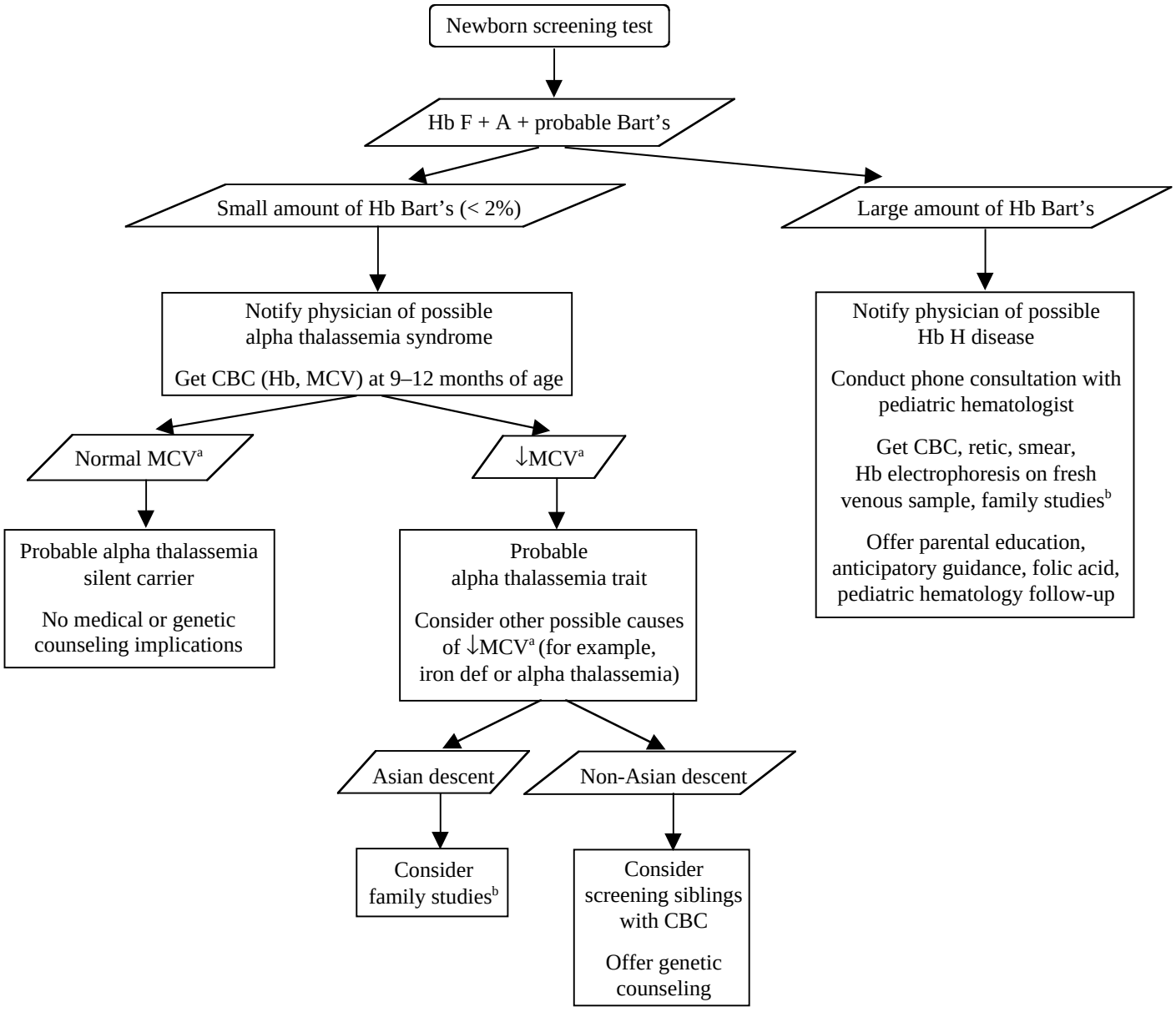
1. **Collect a Sample**
   Collect a sample from all infants using dry blood spots on filter paper or liquid cord blood. Initial testing methods must be of high sensitivity and reasonable specificity.

2. **Report Positive Screening Results and Conduct Confirmatory Testing**
   The newborn screening laboratory reports positive results indicating potential sickle cell disease trait or other hemoglobinopathy trait (FAS, FAC, FAE, FAVariant) to the sample submitter, the newborn screening program follow-up coordinator (who varies by state), and the infant's primary care physician. Confirmatory testing (hemoglobin electrophoresis) is performed in an appropriate laboratory *by 6 months of age.*

3. **Arrange for Education and Genetic Counseling**
   Education and written materials about the hemoglobin trait and its genetic inheritance are provided to the family of the identified infant when a hemoglobinopathy trait has been identified. Education emphasizes the lack of illness associated with these conditions but stresses the potential genetic implications. Family members of the infant identified as having a hemoglobinopathy trait are offered testing, counseling, and education.

Follow-Up Procedures for Infants with Hb Bart's on Neonatal Screen

Hb Bart's is a neonatal hemoglobin composed of 4 gamma chains (γ4); it results from insufficient alpha globin chains. When Hb Bart's is present on newborn screening it may indicate an alpha thalassemia syndrome. Therefore, it deserves special attention. This algorithm indicates the steps that should be considered in a follow-up evaluation.



[a]Normal MCV for infants 9–12 months of age is ≥ 70 fL. A phone consultation with a pediatric hematologist might help in interpreting results.
[b]Initially, perform CBC on parents and other siblings. Subsequent evaluation of couples possibly at risk for hydropic fetus requires DNA studies.

Guidelines for Genetic Counseling Regarding Sickle Cell Disease and Sickle Cell Trait

- A medical specialist or individual trained in genetic counseling for hemoglobinopathies should provide genetic counseling. Counseling can be provided by a genetic counselor with expertise in hemoglobinopathies or by a hematologist, pediatrician, nurse, or other knowledgeable medical specialist.
- Patients with clinically significant disease should already be under the medical management of a primary care physician or pediatrician and hematologist. If possible, all pertinent laboratory tests—newborn screening results (initial and confirmatory), DNA, and other hemoglobinopathy testing—should have been done previously. (For details of testing potential hemoglobinopathy carriers, see the next bullet point.) Additional testing may be recommended after an evaluation of the family history. Depending on each patient's and family member's medical resources, these tests may be ordered immediately after counseling or may need to be arranged individually.
- Genetic counseling information should include review of genetic inheritance (specifically the autosomal recessive mode of inheritance), recurrence risk information, evaluation of the family history, and discussion of the role of testing other family members who are at risk for a hemoglobinopathy. Testing of potential carriers requires a CBC and hemoglobin electrophoresis (including quantitation of Hb F and Hb A_2 if the MCV is borderline or decreased). *Solubility testing is inadequate and should never be used for hemoglobinopathy screening.*
- Information about the clinical course and medical complications of the hemoglobin disorder must be provided, emphasizing the importance of continuing medical follow-up and health maintenance strategies, which can help decrease the number and severity of medical complications.
- If a pregnancy is in progress for a couple at risk for a child with a hemoglobinopathy, the couple should receive a referral to a prenatal genetics center or obstetrician to discuss options for prenatal testing.

References

Diggs LW. Anatomic lesions in sickle cell disease. In Abrahanson H, Berles JF, Wethers DL (eds). *Sickle Cell Disease: Diagnosis, Management, Education, and Research.* St. Louis, Missouri: CV Mosby; 1973:189–229.

Emond AM, Collins R, Darville D, et al. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. *J Pediatr* 1985;107:201–6.

Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. *N Engl J Med* 1986;314:1593–9.

Grover R, Shahidi S, Fisher B, et al. Current sickle cell screening program for newborns in New York City, 1979–1980. *AJPH* 1983;73:249–52.

John AB, Ramlal A, Jackson H, et al. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *Br. Med J* 1984;1567–70.

National Institutes of Health Consensus Development Conference. Newborn screening for sickle cell disease and other hemoglobinopathies. *JAMA* 1987;258:1205–9.

Pearson HA. Aneonatal program for sickle cell anemia. *Adv Pediatr* 1986;3:381–400.
Powars D, Overturf G, Weiss J, et al. Pneumococcal septicemia in children with sickle cell anemia. Changing trend of survival. *JAMA* 1981;245:1839–42.
Seeler RA. Deaths in children with sickle cell anemia. A clinical analysis of 19 fatal instances in Chicago. *Clin Pediatr* 1972;11:634–7.
Thomas AN, Pattison C, Serjent GR. Causes of death in sickle-cell disease in Jamaica. *Br Med J* 1982;285:633–5.

Health Care Maintenance for Children and Adolescents With Sickle Cell Disease

Health care maintenance for children and adolescents with sickle cell disease includes both the standard care (services, evaluations, education, and anticipatory guidance) provided to all pediatric patients and the unique, specialized services and medical and psychosocial care necessary for sickle cell disease. Optimal health care maintenance for the child with sickle cell disease involves an integrated approach from a multidisciplinary health care team of pediatric hematologists, nurses, social workers, psychologists, and genetic counselors working with the primary care provider.

One essential component of care for a child with sickle cell disease is the ongoing consultation and clinical involvement of a pediatric hematologist and/or sickle cell program. The frequency of visits will depend on the needs of the child and family. During the first year of life, frequent visits are essential, because it takes a great deal of time to educate and provide support to the family of children newly diagnosed with sickle cell disease. During the first 2 years of life, schedule health care maintenance visits concurrently with immunizations. Older patients who are doing well can be seen as infrequently as semiannually. The hematologist should also see children shortly after hospitalizations or emergency room visits to review situations that might have precipitated the event and make appropriate changes in the treatment plan.

Health care maintenance includes general pediatric care and subspecialty care at a comprehensive sickle cell center. Comprehensive sickle cell centers work with pediatricians to ensure that the patient receives complete care. Subspecialty care does not replace primary care.

Standard Health Maintenance

- *Immunizations and other tests.* Administer immunizations according to schedules recommended by the American Academy of Pediatrics.
  - Administer to children with sickle cell disease the pneumococcal vaccines (Prevnar and Pneumovax) and *H. influenzae* type b vaccine based on recommendations by the American Academy of Pediatrics and Advisory Committee on Immunization Practices. See tables 2 and 3.
  - Administer immunization against the hepatitis B virus according to standard schedules.
  - Seasonal influenza vaccines are recommended.
  - Conduct periodic skin tests for tuberculosis.
- *Nutrition.* Dietary counseling is an important element of routine health care of the child with sickle cell disease.
  - Encourage breastfeeding.
  - Iron-fortified infant formulas are an alternative and, if needed, can supplement breastfeeding.
  - Do not routinely prescribe supplemental oral iron unless the child has been

documented as iron deficient (indicated by reduced iron stores assessed by reduced serum ferritin level, serum iron level, or iron-binding capacity). Children with hemoglobin SC or hemoglobin S/beta thalassemia are often microcytic in the absence of iron deficiency. Similarly, the incidence of alpha thalassemia is high in the African American population and might produce microcytosis in the absence of iron deficiency.
  - Routinely administering supplementary folic acid might be useful given the active erythropoiesis. It might be particularly indicated if the dietary history reveals inadequate folate intake.
  - Pay particular attention to the diet if education, unmet economic needs, or cultural patterns place the child at risk for dietary deficiencies.
- *Dental care.* All children, including children with sickle cell disease, require regular dental care.
  - A dental evaluation should be carried out every 6–12 months.
  - When indicated and if adequate amounts are not provided in the drinking water, consider supplemental fluoride.
  - Cleaning and dental fillings do not require special care, but to lessen the risk of bacteremia you may precede operative procedures such as extractions and root canal with standard SBE antibiotic prophylaxis.
  - If the patient requires general anesthesia, see "Management of Children with Sickle Cell Disease Undergoing General Anesthesia and Surgery."
- *Hearing and vision screening.* Health maintenance should include routine hearing and vision screening.
  - Because of the risk for retinopathy associated with sickle cell disease (especially in patients with hemoglobin SC), patients should have formal ophthalmologic evaluations every 1–2 years as needed. If visual changes are reported at any age, the patient should have an immediate ophthalmologic evaluation.
  - Because of ocular complications associated with sickle cell disease, children older than 10 years old should see an ophthalmologist annually for a retina examination.
- *Anticipatory guidance and education*.
  - As with all children, anticipatory guidance should include education about home safety, poisoning, and community safeguards.
  - Enuresis is relatively common and probably related to changes in urine concentration. Counsel parents to *not* limit fluid intake before bedtime.
  - Counsel patients and parents about the adverse health effects of tobacco, alcohol, and illicit drugs.
  - Give teenagers information about safe sex practices. If they are sexually active, encourage them to use condoms to prevent getting sexually transmitted disease, including AIDS. Adolescent patients should be referred to an adolescent clinic if appropriate. Adolescent girls should receive counseling about birth control practices.

Table 1 and the following text provide general guidelines for routine health maintenance for children with sickle cell disease. The content of each visit is organized by unique developmental needs appropriate to age. Health maintenance care should follow these guidelines with modifications for individual situations. Frequent visits are essential during the first year of life. Older patients who are doing well may be seen as infrequently as semiannually or even annually if appropriate.

Table 1
Routine Comprehensive Evaluations for Children with Sickle Cell Disease

	Infancy					Early Childhood				Late Childhood	Adolescence
	Neonatal	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	2–5 yr	5–13 yr	13–21 yr
Education	•	•	•	•	•	•	•	•	•	•	•
Genetic counseling	•										
Psychosocial evaluation	•	•	•	•	•	•	•	•	•	•	•
Medical evaluation											
Interim history	•	•	•	•	•	•	•	•	•	•	•
Physical examination	•	•	•	•	•	•	•	•	•	•	•
Laboratory evaluation											
CBC with reticulocyte count	•	•	•	•	•	•	•	•	•	•	•
Hemoglobin electrophoresis	◦			◦ Consider repeat							
Chemistry profile											
Urinalysis											
Quantitative G6PD analysis				◦							
Red blood cell antigenic phenotype				◦							

• Perform with each visit
◦ Perform one time only and document as baseline information
Perform at least annually
Perform on an individual basis as clinically indicated

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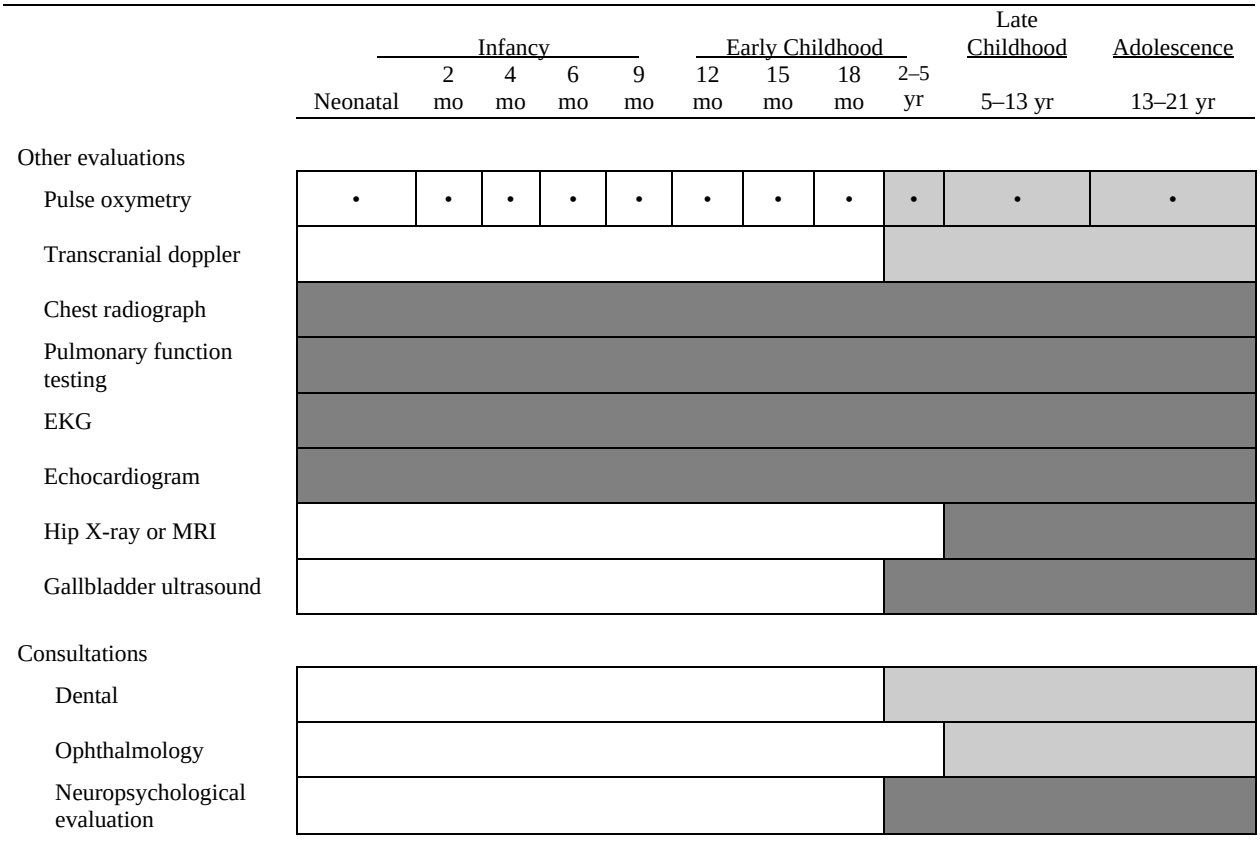
Table 1—*Continued*



• Perform with each visit
◦ Perform one time only and document as baseline information
Perform at least annually
Perform on an individual basis as clinically indicated

Health Maintenance During Infancy (Birth to 12 months)

- Education
  - Diagnosis
    - Once the definitive diagnosis is established, provide the parents with appropriate education and counseling about the specific form of sickle cell disease affecting their child. Provide written information.
    - Explain carefully, avoiding medical jargon and allowing ample time for questions.
    - During initial visits, do not overload parents with too much detail. More than one counseling or education session is required to ensure that parents adequately understand the information. Do not hesitate to refer the patient and family to a specialist for counseling.
    - Inform the parents of available resources, such as the Sickle Cell Disease Association of America and other state and regional agencies.
    - Many community-based sickle cell organizations will help with educating patients and accessing social services.
    - Record the definitive diagnosis on the child's immunization record and in other key medical records. Give a copy of the diagnostic information to the parents for

them to share with other health professionals involved with the infant's care. Give the family a card that identifies the infant to emergency medical services. Consider a medical information bracelet.

- General pathophysiology of the disease and physical signs that indicate the need to seek medical attention
  - Stress the need for immediate medical attention for clinical manifestations that might indicate life-threatening complications due to sepsis and splenic sequestration. Topics to cover include
    - Fever
    - Splenic enlargement and abdominal distension
    - Sudden pallor and listlessness
    - Jaundice
    - Swelling of the hands and feet
    - Respiratory distress
  - Teach the parents how to palpate the spleen. Stress the need to seek immediate medical attention if they think the spleen size has increased or if the child appears pale or listless.
  - Review the signs of pain (especially dactylitis). Instruct the family about managing pain at home (see "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease") and when to seek medical attention.
  - Recognize that parents can assimilate only a limited amount of information about the disease during a single visit. Deliver the essential information and reinforce it incrementally during the course of ongoing care. For example, because pain and stroke are unlikely to occur in the first few months of life, these topics can be covered later.
- Prophylactic penicillin
  - Begin penicillin prophylaxis as soon as diagnosis is suspected and at the latest by 2 months of age.
  - The recommended starting dose of Penicillin V is 125mg orally BID.
  - For patients who are allergic to penicillin, erythromycin ethyl succinate (20mg/kg) divided into two daily doses can provide adequate prophylaxis.
  - *Streptococcus pneumoniae* strains with resistance to penicillin do exist.
- Folic acid
  - Routinely administering supplementary folic acid can be useful, especially if the dietary history reveals inadequate folate intake and for women of childbearing age.
  - The usual dose is 0.5–1mg per day.

- Genetic counseling
  - See "Newborn Screening Follow-Up Guidelines" for genetic counseling regarding hemoglobinopathies and hemoglobin traits).
  - Review genetic inheritance, specifically the autosomal recessive mode of inheritance.
  - Provide information about the risk of recurrence.
  - Evaluate the family history for sickle cell disease and hemoglobinopathies.
  - Discuss the role of testing other family members who are at risk for a hemoglobinopathy. Testing potential carriers requires a complete blood count and hemoglobin electrophoresis (including quantitation of hemoglobin F and hemoglobin

A_2 if the MCV is borderline or decreased). *Solubility testing (sickle cell screen or Sickledex) is inadequate and should never be used for hemoglobinopathy screening.*
  - Provide information about the clinical course and medical complications of the type of sickle cell disease, emphasizing the importance of continuing medical follow-up and health maintenance strategies that can help decrease the number and severity of medical complications.
- Psychosocial evaluation
- Medical evaluation. Perform a complete physical examination, noting
  - Presence or absence of palpable spleen (estimate and record size)
  - Skin color (pallor or jaundice)
  - Presence of a cardiac murmur
- Laboratory evaluation
  - Perform a hemoglobin electrophoresis.
    - When a newborn's screening test indicates sickle cell disease, it is imperative to make a definitive diagnosis. This process requires accurate characterization of the hemoglobin phenotype, which is usually confirmed by performing hemoglobin electrophoresis. Current methods of testing permit diagnostic confirmation of essentially all patients, even in the first months of life. Other types of confirmatory testing include citrate agar (acid) electrophoresis, isoelectic focusing, and high-performance liquid chromatography.
    - *Do not use the sickle solubility test (such as the Sickledex test) to make a diagnosis of sickle cell disease.*
    - Correlate the phenotype with the clinical history, blood counts, and red blood cell morphology.
    - In some cases (hemoglobin variant or suspected alpha or beta thalassemia mutation), it may be necessary to perform DNA-based testing or hemoglobin protein structural analysis.
    - Studies of the child's parents are useful in establishing a definitive diagnosis but must be undertaken with caution, as the tests may disclose mistaken paternity. As in all inherited disorders, thorough counseling of the mother is recommended before performing extensive family testing, and family testing should not be performed if the mother objects.
  - Perform a complete blood count and reticulocyte count.
    - Establish a hemoglobin baseline when the child is well.
    - This value may not be established until the child is several months old and past the physiologic nadir.
  - Perform urinalysis and a chemistry profile including liver and renal function tests.
  - Consider performing a Glucose-6-phosphate dehydrogenase assay as a baseline value. Perform it when the child is well. Consider its value in the context of the degree of reticulocytosis.
  - Obtain an red cell antigenic phenotype (at least C, E, and Kell) after the age of 6 months or before the first anticipated transfusion for baseline information.
- Other evaluations
  - Pulse oximetry
    - Establish a baseline value on room air when the child is well.
    - Repeat and document it at least annually.

- Consider performing a chest X-ray annually in patients with cardiac or pulmonary disease or in patients with a history of recurrent acute chest syndrome.

Health Maintenance for Early Childhood (1 to 5 years)

- Education
  - Review the diagnosis as appropriate, and review the pathophysiology and potential complications. Topics to cover include
    - Fever and signs of sepsis and infection
    - Splenic enlargement and abdominal distension
    - Sudden pallor and listlessness
    - Jaundice
    - Early signs of a vaso-occlusive pain event
    - Respiratory distress, pneumonia, and acute chest syndrome
    - Paresis and other signs of stroke
    - Chronic anemia
  - Review signs and symptoms of medical emergencies and when to seek medical attention.
  - Stress the need to maintain adequate hydration, nutrition, and rest or sleep.
  - Discuss managing pain at home and when to seek medical attention.
  - Review compliance with penicillin prophylaxis. At 3 years of age (approximately 35 pounds), increase the penicillin dose to 250mg orally BID.
  - Assess use of folic acid.
  - Discuss the child's medical condition in relation to preschool and preschool planning.
- Genetic counseling. Review the genetics of sickle cell disease and family planning.
- Psychosocial evaluation
- Medical evaluation
  - Review the child's interim history, discussing recent illnesses (including pain events), hospitalizations, and absence from preschool or school.
  - Perform a complete physical examination at least annually, including
    - Presence or absence of palpable spleen (estimate and record size)
    - Skin color (pallor or jaundice)
    - Presence of a cardiac murmur
- Laboratory evaluation
  - Perform a complete blood count and reticulocyte count at least annually. Establish a hemoglobin baseline when the child is well.
  - Every year, perform urinalysis and a chemistry profile, including liver and renal function tests.
  - In patients who are chronically transfused or have received several transfusions, monitor ferritin frequently as a marker of iron overload. Consider other indicators of iron overload (liver biopsy or bone marrow) individually. See "Chronic Transfusion in Children with Sickle Cell Disease."
- Other evaluations
  - Document the pulse oxymetry value at least annually.
  - Perform a transcranial doppler evaluation annually, beginning at age 2. If the results are abnormal, repeat with a follow-up study in 6 months. If the patient is symptomatic, perform an MRI immediately. See the section Transcranial Doppler

Ultrasonography Screening in Children with Sickle Cell Disease in "Stroke and Acute Neurologic Event in Children with Sickle Cell Disease."

- Consultations
  - Consider a formal neuropsychological evaluation for any child who demonstrates any changes in cognitive functioning that could be associated with a cerebral vascular event. Subtle signs might include a decline in school performance or behavioral changes.

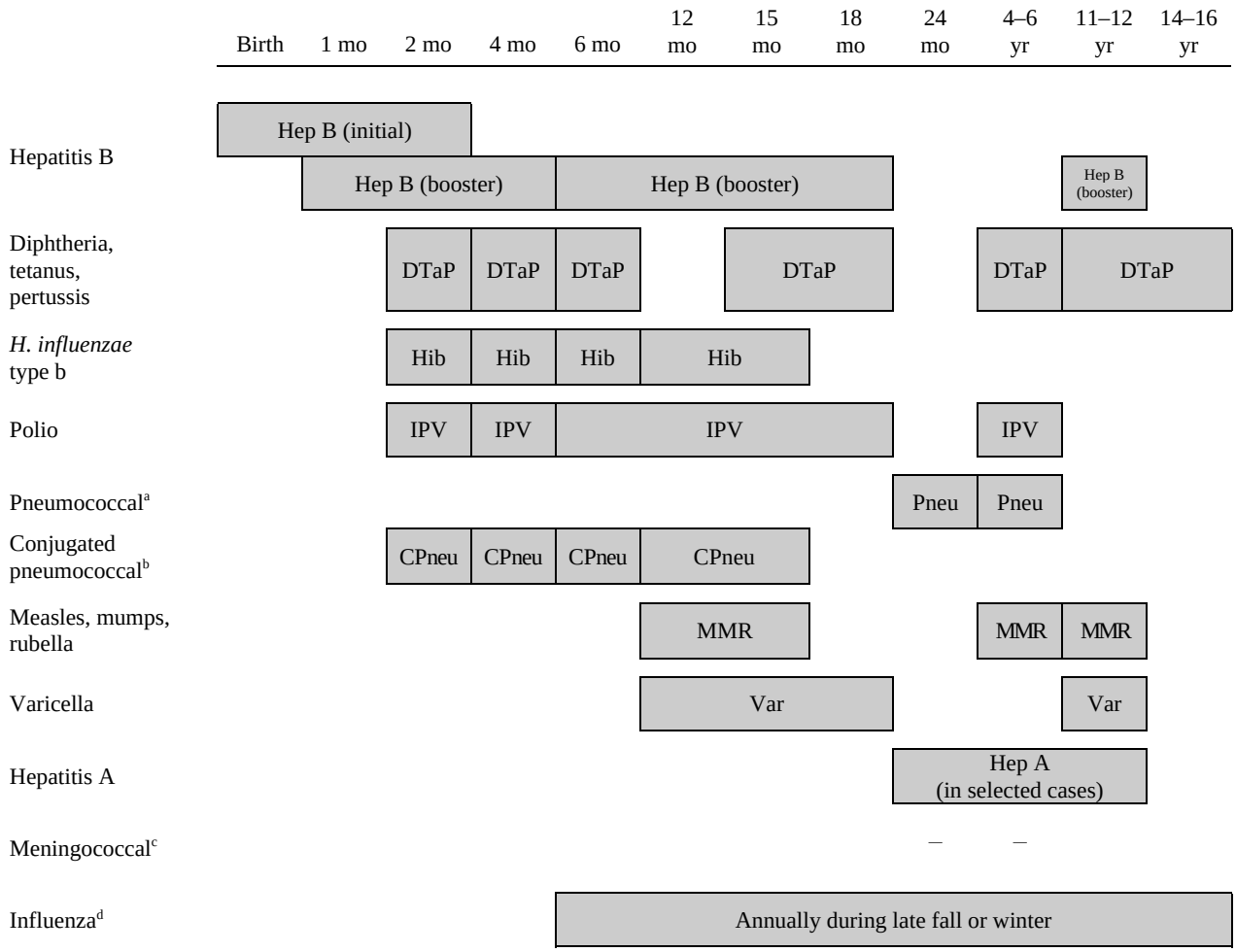
Health Maintenance for Late Childhood (5 to 13 years)

- Education
  - Review potential complications and reinforce signs and symptoms of medical emergencies and when to seek medical attention.
  - Begin to discuss with the child the nature and pathophysiology of sickle cell disease at an age-appropriate level.
  - Discuss managing pain at home and when to seek medical attention.
  - Review and stress the need to maintain adequate nutrition and rest or sleep.
  - Discuss the child's participation in appropriate sports activities. Stress the need for adequate hydration with activity and in hot weather.
  - Administer prophylactic penicillin. Children with sickle cell anemia (SS or Sb^0 thalassemia) who have not had previous severe pneumococcal infections or splenectomies and are receiving comprehensive care may safely stop prophylactic penicillin at 5 years of age. Clinical practice for continuing or not continuing prophylactic penicillin in older children varies significantly; for these patients consider prophylaxis case by case. Give special consideration to children with a history of systemic pneumococcal infections or surgical splenectomy. *If prophylaxis is discontinued, it is imperative to continue prompt medical attention for all fevers.*
  - Review symptoms of priapism.
- Psychosocial evaluation
- Medical evaluation
  - The interim history should include recent illnesses (including pain events), hospitalizations, and absence from preschool or school. Document
    - Recent pain events, including duration, location, quality, and home management
    - Possible avascular necrosis of the femoral head
    - Symptoms of cholelithiasis
    - School attendance and grades, noting any dramatic negative changes in performance that might suggest cerebral vascular disease
  - Perform a complete physical examination at least annually, including
    - Growth and development
    - Skin color (pallor or jaundice)
    - A cardiac murmur
    - A musculoskeletal examination, specifically considering avascular necrosis of the femoral head
    - A complete neurological examination

Health Maintenance for Adolescence (13 to 21 years)

- Education
  - Discuss the nature of the disease with the patient in an age-appropriate manner. Review concerns and issues related to the impact of the disease throughout adolescence.
  - Review the adolescent's school performance.
  - Discuss the adolescent's participation in appropriate sports activities. Stress the need for adequate hydration and rest, especially in hot weather.
  - Discuss the prevention and care of leg ulcers.
  - Review managing pain at home, principles of managing pain, and when to seek medical attention.
  - Review the symptoms of gallbladder disease.
  - Review the symptoms of avascular necrosis of the femoral head.
  - Discuss sexuality and birth control with patients in an age-appropriate manner. Discuss the increased risk of thromboses with some oral birth control medications.
  - Review with female patients pregnancy risks associated with sickle cell disease.
  - Discuss plans for independent living.
  - Provide counseling about education, postsecondary education, and vocational planning.
  - Address concerns about the transition to adult medical care and facilitate the transfer when appropriate and desired.
  - Counsel patients and parents about the adverse health effects of tobacco, alcohol, and illicit drugs.
  - Review the symptoms of priapism.
- Genetic counseling
  - Review the genetics of sickle cell disease with the patient.
  - Discuss the chances of having affected children if the partner is a carrier.
  - Stress the need for carrier testing of the patient's partner and help facilitate testing.
- Psychosocial evaluation
- Medical evaluation. In the interim history and physical examination, cover the points outlined for late childhood, emphasizing
  - Vaso-occlusive pain events
  - Possible avascular necrosis of the femoral head
  - Symptoms of cholelithiasis
  - School attendance and grades, taking note of any dramatic negative changes in performance that might suggest cerebral vascular disease
  - Chronic respiratory changes or findings
  - Growth and development
  - Skin color (pallor or jaundice)
  - Musculoskeletal examination with specific consideration of avascular necrosis of the femoral head
  - Complete neurological examination

Table 2
Recommended Immunizations for Children with Sickle Cell Disease



Source: Based on the American Academy of Pediatrics (AAP) January–December 2000 Immunization Schedule [www.aap.org/family/parents/immunize.htm and *MMWR* 2000;49 (No. RR-9)].

Notes: Range of ages recommended for immunization for all children by the AAP. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible.
Indicates vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.
Specific immunizations recommended for children with sickle cell disease.

[a]One dose of the 23-valent polysaccharide vaccine (PPV23) is administered at 2 years old and at least 2 months after the last dose of the 7-valent pneumococcal conjugate vaccine (PCV7). Regardless of the age of the child when administered, a second dose of PPV23 should not be administered < 3 years after the previous PPV23 dose. If the patient is > 10 years old, 1 vaccination should be administered at least 5 years after the previous PPV23 dose. If the patient is < 10 years, consider 1 vaccination 3–5 years after the previous dose (Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2000;49 (No. RR-9):25. The American Academy of Pediatrics. Pneumococcal Infections. In LK Pickering, ed. *2000 Red Book: Report of the Committee on Infectious Diseases.* 25 ed. Elk Grove Village, Illinois: American Academy of Pediatrics; 2000:459.)
[b]PCV7 is recommended for all children. There are special recommendations for children with sickle cell disease as indicated in table 3. [*MMWR* 2000;49 (No. RR-9):1-27].
[C]The meningococcal vaccine is recommended by the AAP *Red Book*, but it is not considered standard of care at many sickle cell disease centers.
[d]The first set of influenza vaccines consists of 2 injections, 1 month apart. During subsequent years, only 1 injection is given.

Table 3
Recommended Schedule for Use of 7-Valent Pneumococcal Conjugate Vaccine (PCV7) Among Previously Unvaccinated Infants and Children with Sickle Cell Disease by Age at the Time of the First Vaccination

Age at First Dose (in months)	Primary Series	Additional Dose
2–6	3 doses, 2 months apart (for children vaccinated at age < 1 year, the minimum interval between doses is 4 weeks)	1 dose at 12–15 months (administer the additional dose at least 8 weeks after completing the primary series)
7–11	2 doses, 2 months apart (for children vaccinated at age < 1 year, the minimum interval between doses is 4 weeks)	1 dose at 12–15 months (administer the additional dose at least 8 weeks after completing the primary series)
12–59	2 doses, 2 months apart (minimum interval between doses is 8 weeks)	None
> 59	Data are limited on the efficacy of PCV7 among children > 5 years old and adults. However, as PCV7 is immunogenic among children 2–13 years old with recurrent respiratory infections (Sorenson et al.), and as PCV7 is immunogenic among older children and adults 4–30 years old with sickle cell disease (Vernacchio et al.), seriously consider administering PCV7 to older children with sickle cell disease.	

Source: MMWR 2000;49 (No. RR-9):1–27.

References

American Academy of Pediatrics Committee on Genetics. Health Supervision for Children with Sickle Cell Disease. *Pediatrics* 98:467–72;1996.

Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. *J Pediatr* 1995;127:685–90.

National Institutes of Health, National Heart, Lung and Blood Institute, Child and Adolescent Health Care Maintenance. Chap. 1 in *Management and Therapy of Sickle Cell Disease,* NIH Publication No. 95-2117. 3d ed, rev. December 1995.

Sorenson RU, Leiva LE, Giangrosso PA, et al. Response to heptavalent conjugate *Streptoccoccus pneumoniae* vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. *Peditr Infect Dis J* 1998;17:685–91.

Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr* 1998;133:275–8.

Evaluation and Initial Management of Acute Chest Syndrome In Children with Sickle Cell Disease

Acute chest syndrome is characterized by chest pain, dyspnea, hypoxemia, fever, prostration, and the appearance of a new pulmonary infiltrate on a chest X-ray. Initially, only some of these signs and symptoms might be present; X-ray changes can take several days to appear. Although the illness can be self-limited, particularly when it involves a small area of pulmonary parenchyma, it can progress rapidly and be fatal. Frequent acute chest syndrome episodes indicate severe sickle cell disease, and it is among the leading causes of death in patients with sickle cell disease.

Although the etiology can vary, it is useful to group together sickle cell patients with a new chest X-ray infiltrate under the term *acute chest syndrome;* they possess common features with implications for management. Because it is often difficult to distinguish infection from infarction, it is important to institute treatment for both regardless of etiology. In children, an infectious etiology is often considered, but in many cases a specific cause is not identified. Acute chest syndrome can result from infection, pulmonary infarction, fat or bone marrow embolism, intrapulmonary sickling, and emboli of sickled red cells. According to recent bronchoscopy and bronchial lavage data, pulmonary fat embolism occurs in as many as 44% of patients with acute chest syndrome.

Acute chest syndrome can develop as an isolated event or during the course of a painful vaso-occlusive episode. Often, a dominant symptom is pleuritic chest pain. In infants and young children, often the only findings are fever, cough, and tachypnea. If the diaphragmatic pleura are affected, it can cause abdominal pain. True lung pathology must be differentiated from sternal or rib infarction or cholecystitis. Although the pain of acute chest syndrome can mimic angina or myocardial infarction, coronary artery disease is rare in children and young adult patients. Physical examination usually shows tachypnea, and there may be signs of pulmonary consolidation, pleural effusion, or, occasionally, a pleural friction rub. A change in mental status might reflect hypoxemia and/or narcotic effect, but it is also seen in patients with systemic fat embolization or stroke (see “Stroke and Acute Neurological Event in Children with Sickle Cell Disease”).

- ***Do not delay antibiotic administration if the patient is febrile.*** **See “Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease.”**
- **Because acute chest syndrome is a life-threatening emergency, consult with a pediatric hematologist with expertise in sickle cell disease.**
- **If the patient is hypoxic, has a diffuse pulmonary infiltrate on a chest X-ray, or has a history of life-threatening acute chest syndrome, immediately transfer the patient to a medical center with expertise in sickle cell disease and capability in pediatric intensive care.**

1. **Initial Contacts**
    - Tell the family and patient to contact the primary care physician or hematologist if the child develops a cough, respiratory distress, fever, or chest pain so the child can be promptly evaluated in a clinic or emergency department (ED).
    - As soon as the patient presents at the physician's office, clinic, or ED, evaluate the patient and begin treatment immediately as described below.
    - To facilitate triage, the referring physician or hematologist should immediately inform the ED staff that the child will be arriving and provide relevant clinical information.
    - If the child presents at the ED without a physician referral, the ED staff should contact the primary care provider or pediatric hematologist responsible for the child's care to obtain background information and ensure appropriate medical management.

2. **History**
    - Consider symptoms of fever, cough, labored breathing, wheezing, and chest pain.
    - Document associated symptoms including pain, especially bone pain of an extremity, because of acute chest syndrome's association with fat and bone marrow embolism. Consider upper abdominal pain, as it can be a symptom associated with a lower lobe pneumonia.
    - Review the history of oxygen requirement. Try to determine patient's baseline oxygen saturation measurement.
    - Review the history of reactive airways disease (asthma).
    - Review current medications, including any inhalant medications used for reactive airways disease (asthma).
    - Document drug allergies.
    - Review recent infectious exposures.
    - Review the medical history, focusing on problems related to sickle cell disease, especially lung problems. Question whether the patient has had acute chest syndrome, pneumonia, or any previous hospital admissions that might have involved respiratory problems.
    - Review the last comprehensive evaluation and/or baseline information from the patient's hematologist or sickle cell disease treatment center as soon as possible.

3. **Initial Physical Examination**
    - Measure oxygen saturation by pulse oximetry (room air and with supplemental oxygen).
    - Take vital signs, including blood pressure.
    - Pay particular attention to the chest examination, documenting respiratory rate, effort, and breath sounds.
    - Measure the degree of pallor.
    - Look for evidence of sepsis such as chills, rigors, diminished peripheral perfusion, cool extremities, or localized infection.
    - Check cardiovascular status.
    - Conduct an abdominal examination with attention to localized findings in the upper quadrants, which might indicate a lower lobe pneumonia.
    - Conduct a neurologic exam with attention to alertness state, degree of sedation, and orientation.

4. Diagnostic Evaluation

- Get a stat complete blood count (including WBC differential and platelet count) and reticulocyte count.
  - Compare these counts with the patient's baseline values.
  - Obtain serial complete blood counts, including reticulocyte counts and leukocyte differential counts.
  - An increased neutrophil count above the baseline level and a shift to the left suggests a bacterial infection.
  - A falling hematocrit, with or without reticulocytosis, is commonly seen as the syndrome evolves and can contribute to tissue hypoxia.
- Get a stat chest X-ray.

Consider performing serial X-rays based on clinical status. Frequently, radiographic studies in the first 2 to 3 days are normal or nondiagnostic; in these cases the condition is diagnosed only later by clinical signs as it evolves.

  - The chest X-ray of patients with acute chest syndrome might show infiltrates in one or more lobes (66% of cases involve a single lobe).
  - Pleural effusion occurs in 15% of cases.
- Lung scans generally are not useful in diagnosing the etiology of acute chest syndrome or in making a therapeutic decision. Due to the hypertonicity of most contrast dyes, pulmonary angiography carries the theoretical risk of increased sickling; therefore, the procedure is rarely indicated.
- Get a blood culture if the patient is febrile or has a recent history of fever.
- Consider other cultures. Cultures of sputum or pleural fluid occasionally reveal a bacterial pathogen.
- Consider performing Mycoplasma titers and/or cold agglutinins and nasal washings for viral pathogens. Isolation of Mycoplasma or viruses or a rise in antibody titers might help suggest the etiology. A viral etiology is more likely in winter; Mycoplasma are more common in the fall.
- If sputum or bronchial lavage specimens are obtained, stain them for fat. A positive result suggests fat embolism.
- Get a type and screen/cross match requesting sickle-negative and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for types C, E, and Kell is recommended.
- Consider arterial blood gas (ABG) based on clinical condition. If noninvasive oximetry is used to monitor trends, it is most helpful in conjunction with periodic ABG measurements.
- For initial assessment of the illness's severity and subsequent clinical management, it might be necessary to measure arterial blood gases rather than pulse oximetry. Take initial samples while the patient is breathing room air.
- Because some patients with sickle cell disease have a low arterial oxygen pressure (PaO_2) during the steady state, interpreting low oxygen tension can be difficult unless ABG measurements were obtained earlier. However, severe hypoxemia (PaO_2 < 60mm Hg in an adult or < 70mm Hg in a child) indicates potentially life-threatening disease,

particularly if it does not improve with oxygen administration.

- In patients receiving oxygen by face mask, assess the severity of the pulmonary process by calculating the A-a O_2 gradient.
- In cases of severe illness or encephalopathy, consider a chemistry profile to assess renal (BUN and Creatinine) and liver function (fractionated bilirubin, ALT, and AST).
- Consider bronchoscopy for selected patients.

5. Management

All patients with acute chest syndrome must be admitted to the hospital. Depending on the extent of lung involvement and respiratory distress, the intensive care unit might be required for appropriate monitoring of a rapidly changing clinical state. Because acute chest syndrome is a life-threatening emergency, consult a pediatric hematologist with expertise in sickle cell disease. If the patient is hypoxic, has diffuse pulmonary infiltrate on a chest X-ray, or has a history of acute chest syndrome, consider immediate transfer to a medical center with expertise in sickle cell disease.

- Administer oxygen therapy for hypoxemia, tachycardia, and tachypnea.
  - Monitor with continuous pulse oxymetry and consider measuring arterial blood gases if clinically indicated.
  - Provide oxygen therapy to maintain oxygen saturation ≥ 94% (or enough to keep at the baseline pulse oximetry percentage). Adjust oxygen delivery as needed for the patient's comfort and cardiovascular stability.
  - Monitor the use of oxygen masks. Patients can become profoundly hypoxic if they remove their oxygen masks for eating or bathing. Nasal prongs can be used in these instances, but the amount of oxygen the patient inspires will be lower than with a face mask.
- Administer analgesics. (See "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease" for specific information about management.) However, narcotic-induced hypoventilation must be avoided. Find a delicate balance to provide pain relief and eliminate splinting without causing hypoventilation.
- Monitor hydration. Overhydration can be as dangerous as dehydration, and intravenous fluids must be cautiously administered.
  - Administer hydration using oral and intravenous fluids. Total hydration (oral, intravenous, and medications) should not exceed a 1–1½ times maintenance rate. Increased fluids might be needed if the patient is dehydrated or if insensible losses such as persistent fever are increased.
  - If signs of fluid overload are present, consider judicious administration of a diuretic such as Lasix.
- Consider a trial of bronchodilators and/or steroids, especially if the patient has history of reactive airway disease or wheezing on exam.
- Administer antibiotic therapy.

It is often impossible to make a reliable a priori differentiation between pulmonary infarction and bacterial pneumonia. In 2–5% of cases, acute chest syndrome is associated with a positive blood culture; the most common isolates are *S. pneumoniae* and *H. influenzae.*

  - Use an appropriate combination of penicillin, cephalosporin, and vancomycin depending on the local susceptibility pattern of *S. pneumoniae* and *H. influenzae* and whether the patient was on prophylactic penicillin. See "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease" for information about antibiotic dosing.
  - If Mycoplasma pneumonia or Chlamydia is suspected, consider adding a macrolide antibiotic.
  - Adjust the antibiotic regimen based on the results of the bacterial cultures.
  - Discontinue prophylactic penicillin while the patient is on broad-spectrum antibiotics.
- Consider a red blood cell transfusion for progressive clinical deterioration. For moderately severe illness, consider simple red cell transfusion (instead of exchange transfusion) using packed red blood cells for moderately severe illness.

- **Before starting transfusion therapy, consult a pediatric hematologist with expertise in sickle cell disease.**
- **If the clinical condition warrants transfusion therapy, transfer patients to the intensive care unit of a medical center with expertise in sickle cell disease.**
- **Rapid increases in the hemoglobin level can cause hyperviscosity that might contribute to the worsening of the clinical condition.**

  - If the patient develops multiple lobe involvement, rapidly progressing disease, or signs of respiratory insufficiency (PaO_2 < 60mm Hg in an adult or < 70mm Hg in a child while breathing oxygen), perform exchange transfusions. Consider patients with chronic hypoxemia, as determined by baseline studies, for exchange transfusions when there is a drop of > 25% from the steady-state PaO_2.
- Monitoring.
  - Monitor with continuous pulse oxymetry.
  - Measure vital signs including blood pressure at least every 4 hours, more frequently as indicated.
  - If the patient is in pain, assess and record pain intensity at least every 4 hours using an age-appropriate pain-intensity-measurement instrument. See "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease" for specific information.
  - Record accurate intake and output and daily weight as clinically indicated.
  - If they are clinically indicated and if any respiratory symptoms suggest oversedation while receiving parenteral opioids, consider a cardio-respiratory monitor and continuous pulse oximetry.

- General care.
  - Perform incentive spirometry; it is extremely important. During the daytime hours when awake, the patient should use the spirometer for at least 10 breaths every 2 hours. To promote rest, wake the sleeping patient every 4 hours during the day to perform incentive spirometry. During the night, wake the patient every 4 hours.
  - Consider physical therapy if the patient is able to participate.
  - Consider chest physiotherapy if the patient tolerates it. Repositioning the patient might also help with respiratory status.
  - Encourage ambulation and light activity if the patient tolerates it.
  - If the patient is in pain, offer heating pads and other comfort measures.
- Other diagnostics during hospital admission.
  - Perform a complete blood count, platelet count, and reticulocyte count initially and as clinically indicated. Compare these values with the patient's baseline data.
  - Consider performing serial X-rays until an infiltrate is apparent or stabilizes, or if either of the following develop after admission:
    - Worsening chest pain
    - Progressive respiratory distress including increase oxygen requirement and worsening tachypnea
  - If the patient is febrile, see "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."
  - If parenteral opioids or antibiotics are used as clinically indicated, consider renal (BUN, Creatinine) and liver (fractionated bilirubin, ALT, and AST) function tests.
  - To rule out cholelithiasis, cholecystitis, and pancreatitis, consider an abdominal ultrasound, liver function tests, and/or amylase and lipase for severe epigastric or right upper quadrant abdominal pain.
- Other medications.
  - See "Evaluation and Management of Acute Pain In Children with Sickle Cell Disease," table 5, about treating possible side effects associated with opioid treatment.
    - For narcotic-induced constipation, consider a stool softener such as docusate sodium (Colace). In some cases, additional laxatives are required.
    - For opioid-induced pruritus, use antihistamines such as diphenhydramine (Benadryl).
    - For opioid-induced nausea, Ondansetron hydrochloride (Zofran) or another antiemetic might be useful.
  - Consider antipyretics. It is a common concern that antipyretic therapy might mask fever and make a clinical decision more difficult. However, once the decision has been made to start antibiotic therapy, seriously consider the beneficial effects of antipyretics on the febrile patient with sickle cell disease.
- Other considerations.
  - See other specific guidelines for managing acute concomitant complications associated with sickle cell disease, such as fever, pain, acute splenic sequestration, aplastic crisis, stroke, and priapism.
  - Complications associated with acute chest syndrome include
    - *systemic fat embolization syndrome,* a rare but often fatal complication caused by widespread embolization of liquefied necrotic bone marrow fat into the

pulmonary vessels and then into the systemic circulation. Patients with sickle cell disease can develop the syndrome during a severe vaso-occlusive episode. Symptoms include bone pain, fever, chest pain, dyspnea, confusion, agitation, and coma, with or without acute renal failure. In some cases disseminated intravascular coagulation with severe microangiopathic hemolytic anemia and multiorgan failure can occur. For early diagnosis, it is essential to maintain a high index of suspicion. Pulmonary fat embolization can be detected by finding intracellular lipid in secretions obtained by bronchial lavage. Other findings helpful in establishing the diagnosis include necrosis on marrow aspirates, refractile bodies on fundoscopic examination, head and neck petechiae, and fat globules in the urine. If the syndrome is suspected, begin exchange transfusions accompanied by supportive treatment early on; this approach might be lifesaving.

- *asthma and chronic asthmatic bronchitis,* which pose a potential therapeutic problem in sickle cell disease patients. Epinephrine use is associated with increasing heart rate and can compromise cardiac stroke output. Although bronchodilators are usually required, these agents have a diuretic action that can dehydrate the patient. To alleviate this effect, hydration is essential. Administer intravenous fluids early during an asthma attack that does not quickly resolve. Long-term management is the same as for individuals without sickle cell disease.
- *chronic restrictive lung disease,* with pulmonary hypertension and cor pulmonale in late stages. This disease is a consequence of previous vaso-occlusive episodes and has a poor prognosis. Diagnosis before the clinical onset of cor pulmonale is based on abnormal pulmonary function tests, a chest radiograph demonstrating increased parenchymal markings or fibrosis, and chronic hypoxia. Repeated episodes of midline, severe, crushing chest pain signal myocardial ischemia (without coronary artery disease). With recurrent episodes of acute chest syndrome, the patient develops pulmonary hypertension and heart failure. A chronic transfusion program can reduce the frequency of recurrent attacks of chest syndrome, and nocturnal oxygen therapy can be helpful to some patients.

6. Recommended Discharge Criteria

- Adequate oxygenation on room air or back to baseline oxygenation
- Afebrile ≥ 24 hours and presenting no evidence of infection
- Able to take adequate oral intake, including oral medications if needed
- Adequate pain relief (if needed) with oral analgesics

7. Outpatient Management, Discharge Considerations, and Recommended Follow-Up

- Ensure that the patient has access to appropriate analgesic medication for home use if needed.

Coordinate a clear follow-up plan with the hematology service, including

- **A return visit to the sickle cell disease clinic in 2–3 weeks**
- **A plan for breakthrough pain**
- **Directions for resuming normal age-appropriate activities**
- **Other follow-up plans**

Summary: Causes of Acute Chest Syndrome

- **I. Related to sickle hemoglobin (Hb S)**
  - A. Direct consequence
    - 1. Pulmonary infarction—in situ sickling
      - *a*) Etiology unknown
      - *b*) Hypoventilation secondary to
        - (1) Rib/sternal infarction
        - (2) Narcotic administration
        - (3) Postoperative atelectasis
    - 2. Embolism infarction
      - *a*) Necrotic bone marrow/fat
      - *b*) Sickled cells from distal site (such as liver sinusoids)
    - 3. Pulmonary edema secondary to fluid overload
  - B. Indirect consequence—infection
    - 1. Bacterial
    - 2. Viral
    - 3. Fungal
    - 4. Protozoan
- **II. Unrelated to sickle hemoglobin (Hb S)**
  - A. Thromboembolism (from thrombosed vein)
  - B. Opportunistic infection related to HIV infection
  - C. Bronchial obstruction secondary to foreign body or neoplasm
  - D. Acute sarcoidosis
  - E. Other (such as aspiration and trauma)

References

Bellet P, Kalinyak K, Shakla S, et al. Incentive spirometry to prevent acute pulmonary complication in sickle cell disease. *N Engl J Med* 1995;333:699–703.

Bhalla M, Abboud MR, McLoud TC, et al. Acute chest syndrome in sickle cell disease: CT evidence of microvascular occlusion. *Radiology* 1993;187:45–9.

Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood* 1994;84:643–9.

Gelfand MJ, Daya SA, Rucknagel DL, et al. Simultaneous occurrence of rib infarction and pulmonary infiltrates in sickle cell disease patients with acute chest syndrome. *J Nuclear Med* 1993;34:614–8.

Johnson CS, Verdegem TD. Pulmonary complications of sickle cell disease. *Semin Resp Med* 1988;9:287–96.

National Institutes of Health, National Heart, Lung and Blood Institute. Lung. Chap. 8 in *Management and Therapy of Sickle Cell Disease*, NIH Publication No. 95-2117. 3d ed, rev. December 1995.

Powars D, Weidman JA, Odom-Maryon T, et al. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine* 1988;67:66–76.

Sprinkle RH, Cole T, Smith S, et al. Acute chest syndrome in children with sickle cell disease. A retrospective analysis of 100 hospitalized cases. *Am J Pediatr Hematol Oncol* 1986;8:105–10.

Vichinsky E, Williams R, Das M, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. *Blood* 1994;83:3107–12.

Aplastic Crisis
In Children with Sickle Cell Disease

Aplastic crisis is an acute illness characterized by a significant decrease in the patient's baseline hemoglobin and reticulocyte count. Occasionally, the platelet or WBC count also decreases. Aplastic crises are usually self limited and frequently follow viral infections, most commonly Parvovirus B19. If the spleen is acutely enlarged, consider coexistent splenic sequestration (see "Evaluation and Management of Acute Splenic Sequestration in Children with Sickle Cell Disease").

1. Initial Contacts

- Instruct families and patients to contact their primary care physician or hematologist if the child exhibits fever, pallor, fatigue, or malaise.
- Consider obtaining blood samples for Parvovirus IgM and IgG titers from family members and close contacts with a history of sickle cell disease or other hemolytic anemias at time of presentation and again in 2 weeks. (See Recommended Discharge Follow-Up, below.)
- Tell family members and staff that the patient may have an infectious disease that can cause problems for a fetus. An effective approach to preventing the spread of the disease is respiratory and contact isolation.

2. History

- Duration of pallor
- Change in exercise tolerance or recent onset of lethargy, dyspnea, tachypnea, or tachycardia
- Antecedent or current infection, rash, or temperature elevation
- Medication history
- History of any coexistent significant illnesses other than sickle cell anemia

3. Initial Physical Exam

- Vital signs (including blood pressure and pulse oximetry, if available)
- Cardiopulmonary status
- Degree of pallor
- Liver and spleen size

4. Diagnostic Evaluation

- Complete blood count, including differential, platelet, and reticulocyte count (compare with patient's baseline) initially and then every 12–24 hours, or more frequently if clinically indicated.
- Parvovirus IgM and IgG titers.
- Type and screen/cross match; request sickle-negative and leukocyte-depleted packed red blood cells. If available, request minor antigen-matched blood or blood negative for types C, E, and Kell.
- Consider a chest radiograph for signs of respiratory illness or cardiovascular compromise.

- Blood culture, urine analysis, and urine culture if febrile. See "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."

5. Management

- Admit to hospital for significant decrease in baseline hemoglobin > 1.5–2g/dl) with a low reticulocyte count.
- Consider respiratory isolation (and pregnancy precautions) for presumed Parvovirus infection.
- Consider admitting to ICU for signs of cardiovascular compromise or hemoglobin < 4–5g/dl.
- Check vital signs every 2 hours until stable, then every 4 hours.
- Consider cardio-respiratory monitor.
- Continuous pulse oximetry.
- Maintenance fluids (oral and IV). Increase for insensible losses secondary to fever, etc. Avoid excessive fluids, which may precipitate congestive heart failure.
- RBC transfusion for symptomatic anemia or hemoglobin < 5g/dl with no evidence of erythroid recovery (persistent reticulocytopenia and/or progressive decrease in hemoglobin). Slowly transfuse with small aliquots, such as 5–6cc/kg of packed RBC over 3–4 hours, to avoid fluid overload. Repeat transfusion may be necessary.
- Supplemental oxygen for cardiovascular compromise or to keep oxygen saturation > 92% or greater than patient's baseline value, or empirically for severe anemia requiring transfusion therapy.
- In life-threatening anemia, 100% oxygen might be indicated.
- Prompt treatment of fever with acetaminophen or ibuprofen, since hyperthermia increases heart rate and oxygen consumption and might induce cardiovascular compromise in a severely anemic child.
- Broad-spectrum antibiotic(s) for fever. See "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."
- If the patient is afebrile, continue prophylactic penicillin (or, if the patient is allergic to penicillin, another antibiotic).
- Continue folic acid.

6. Recommended Discharge Criteria

- Stable hemoglobin
- Afebrile for more than 24 hours, with stable vital signs
- Taking oral fluids and medication(s) well

7. Recommended Discharge Follow-Up

- Complete blood count and reticulocyte count once a week, or more often if clinically indicated, until hemoglobin and reticulocyte count approximate normal baseline for the patient.
- If Parvovirus IgM and IgG titers were negative initially, repeat.
- Consider obtaining blood samples for Parvovirus IgM and IgG titers from siblings and close contacts with a history of sickle cell disease or other hemolytic anemias at time of presentation and again in 2 weeks.

References

Emond AM, Collis R, Darvill D, et al. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. *J Pediatr* 1985;107:201.

Kinney TR, Ware RE, Schultz WH, et al. Long-term management of splenic sequestration in children with sickle cell disease. *J Pediatr* 1990;117:194.

Pattison JR, Jones SE, Hodgson J, et al. Parvovirus infections and hypoplastic crises in sickle cell anemia. *Lancet* 1981;1:644.

Seeler RA, Shwiaki MZ. Acute splenic sequestration crises in young children with sickle cell anemia. *Clin Pediatr* 1972;11:701.

Serjeant GR, Serjeant BE, Thomas PW, et al. Human parvovirus infection in homozygous sickle cell disease. *Lancet* 1993;341:1237-40.

Topley AM, Rogers DW, Stevens MCG, et al. Acute splenic sequestration and hyper-splenism in the first five years in homozygous sickle cell disease. *Arch Dis Child* 1981;56:765.

Chronic Transfusion
In Children with Sickle Cell Disease

Blood transfusion plays an integral part in managing sickle cell disease in children, but it should be used as judiciously as possible. Transfusion complications for sickle cell patients are the same as or greater than those for any patient receiving a blood transfusion, acute or chronic. Because of these complications, such as a high incidence of alloimmunization and iron overload, the hematologist, the patient, and the family should carefully consider the decision to begin a chronic transfusion program. Once a program is initiated, patients should be carefully monitored.

The aim of a chronic transfusion program is to decrease the number of red blood cells in the bloodstream by suppressing the bone marrow production of sickle cells. This result can usually be achieved by maintaining the hemoglobin S level at < 30% with a pretransfusion hemoglobin level at > 9–10g/dl. These levels can be reached by providing simple transfusions every 2–4 weeks. For certain clinical situations a higher or lower target level of hemoglobin S might be indicated.

It is strongly recommended that a pediatric hematologist knowledgeable in sickle cell disease institute and supervise all chronic transfusion therapy.

The following are generally considered indications for red blood cell transfusion in children with sickle cell disease:

- **Strongly Recommended Indications**
  - Neurologic complications including stroke, transient ischemic events, or abnormal TCD
  - Severe or recurrent acute chest syndrome
  - Recurrent, debilitating pain
  - Severe chronic anemia with high-output cardiac failure
  - Chronic organ failure

- **Other Indications**
  - Selected pregnancy
  - Progressive MRI anomalies and/or progressive deterioration of psychometric testing
  - Intractable leg ulcer
  - Pulmonary hypertension
  - Recurrent splenic sequestration
  - Recurrent priapism

1. **Initial Contacts**
   - Explain to the family and patient the need for chronic transfusion to prevent stroke, splenic sequestration, vaso-occlussive crisis, and acute chest syndrome.
   - Inform them that transfusion will occur every 2–4 weeks.
   - Inform them about the importance of maintaining the transfusion regimen.

- Educate them about the risks of transfusion therapy.
- Educate them about possible delayed transfusion reaction.
- Obtain current transfusion consent before beginning the transfusion program.
- Instruct them to report to the outpatient clinic at least 24 hours before an anticipated transfusion for a complete blood count with reticulocyte count, as well as type and screen/cross match (10–15cc/kg of leukodepleted PRBCs).

2. History

- Document the indication(s) for chronic transfusion.

3. Initial Physical Examination

- Vital signs including blood pressure and pulse oximetry
- Height and weight
- Cardiopulmonary status
- Spleen size

4. Diagnostic Evaluation

- Before initiating a transfusion program
  - Blood type with phenotype
  - Ferritin
  - Hepatitis panel (A, B, and C) and yearly
  - Hepatitis A and B immunization status
  - HIV status
  - Liver enzymes
  - Consider an audiologic and ophthalmologic evaluation
  - EKG/ECHO
- Before each transfusion
  - Height, weight, vital signs, and oxygen saturation
  - Complete blood count with reticulocyte count
  - Consider hemoglobin electrophoresis to establish a pattern to obtain a goal of hemoglobin S
  - Type and screen/cross match for 10cc/kg of leukodepleted PRBC, antigen matched if available
- During transfusion
  - Height, weight, history, and complete physical exam at least every 3 months
  - Liver enzymes, urine analysis every 6 months
  - Hepatitis panel (A, B, C) yearly
  - Thyroid function, fasting blood glucose, and other endocrine studies as indicated
  - Consider EKG/ECHO yearly and before desferoxamine therapy.
  - Consider HIV testing

5. Management

- The frequency of transfusion is designed for each patient according to the total hemoglobin and hemoglobin S concentration of the past 2 transfusions and the lapsed time since the most recent transfusion. Transfusion is typically provided every 3–4 weeks.

- Erythrocytapheresis must be carried out by qualified personnel. A hematologist needs to evaluate the patient to determine the option of chronic exchange versus chronic pheresis.

> **Hyperviscosity might contribute to worsening of the clinical condition. To avoid hyperviscosity in transfusion with sickle cell patients, do not transfuse to a hemoglobin > 12g/dl. See "Stroke and Acute Neurologic Event in Children with Sickle Cell Disease."**

- Blood administration
  - Determine the amount of blood to be given (usually 10–15cc/kg) by reviewing the hemoglobin level and the reticulocyte count before the transfusion.
  - If the patient has experienced fever, hives, or any allergic manifestation during or following a previous blood transfusion, administer pretransfusion medication, including acetaminophen and an antihistamine, one half-hour before the transfusion.
  - A simple transfusion is given over 3–4 hours with monitoring of vital signs.
  - Document any untoward event in the patient's chart and notify the blood bank.
  - Document the amount of red blood cell volume administered.
- Blood products
  - Screen all blood and confirm negative for the presence of sickle hemoglobin.
  - Use leukodepleted red blood cells to reduce white blood cell and cytomegalovirus contamination.
  - Use washed red blood cells in patients with a history of severe allergic reactions following transfusions.
  - Determine the antigenic phenotype of the red cells in all patients older than 6 months. Keep the record in the blood bank and give a copy to the patient or family.

6. Recommended Follow-Up

- Monitor for iron overload. Measure ferritin at least every 6 months. If available, obtain a hepatic biopsy for hepatic iron content if ferritin is above 15g/ml.

> **Ferritin might not be a reliable measure of iron overload.**

Chelation Therapy

- Monitor the serum ferritin levels at least every 6 months. When the ferritin level reaches 1,500–2,000ng/ml or when hepatic iron content is > 4mg/g of dry weight liver tissue, consider chronic chelation therapy.
- To determine the amount of iron excretion, perform a challenge with desferoxamine (if available). Compare the amount of iron excreted in urine for 24 hours before and after the challenge. Patients excreting more than 5mg of iron in the urine after a desferoxamine challenge should be started on long-term chelation therapy.
- In addition to the diagnostic procedures for chronic transfusion, monitoring should include the following:
  - Audiology yearly and if any symptoms (such as tinnitus or difficulty hearing) are present

  - Ophthalmology yearly or for any new visual symptoms
  - Consider metaphyseal and spinal radiographs

Desferoxamine Therapy

- Consider supplementing with ascorbate, 100–250mg, at the start of each dose of desferoxamine
- Subcutaneous administration
  - Desferoxamine is given SC over 10–12 hours.
  - Usual dose is 20–40mg/kg/day to a maximum of 2g/day for 4–7 days.
- Intravenous administration
  - Consider IV desferoxamine for patients
    - With ferritin > 2,500ng/ml with persistent liver enzyme elevation
    - Who are noncompliant, with ferritin > 5,000ng/ml
    - Who have cardiac arrythmia or evidence of congestive heart failure
    - With progressive iron overload despite subcutaneous treatment
    - Who cannot tolerate subcutaneous desferoxamine treatment
  - Dosage IV should not exceed 15mg/kg/hour for 12 hours/day
- Complications of desferoxamine therapy
  - Otoxocity
  - Ophthalmic toxicity
  - Allergic reactions
  - Growth failure
  - Infection (Yersinia, fungi). During acute bacterial infections, discontinue desferoxamine therapy.
  - Pulmonary hypersensitivity
  - Poor compliance

References

Ambruso DR, Githens JH, Alcorn R, et al. Experience with donors matched for minor blood group antigens in patients with sickle cell anemia who are receiving chronic transfusion therapy. *Transfusion* 1987;27:94.

Bischoff RJ, Williamson A III, Dalali MJ, et al. Assessment of the use of transfusion therapy perioperatively in patients with sickle cell hemoglobinopathies. *Ann Surg* 1988;207:434–8.

Brittenham GW, Cohen AR, McLaren CE, et al. Hepatic iron stores and plasma ferritin concentration in patients with sickle cell anemia and thalassemia major. *Am J Hematol* 1993;42:81–5.

Castro O, Finke-Castro H, Coats D. Improved method for automated red cell exchange in sickle cell disease. *J Clin Apheresis* 1986;3:93–9.

Cohen A. Treatment of transfusional iron overload. *Am J Pediatr Hematol Oncol* 1990;2:4–8.

Cohen AR, Martin MB, Silber JH, et al. A modified transfusion program for prevention of stroke in sickle cell disease. *Blood* 1992;79:1657–61.

Comer GM, Ozick LA, Sachdev RK, et al. Transfusion-related chronic liver disease in sickle cell anemia. *Am J Gastroenterol* 1991;86:1232–4.

Cox JV, Steane E, Cunningham G, et al. Risk of alloimmunization and delayed hemolytic transfusion reactions in patients with sickle cell disease. *Arch Intern Med* 1988;148:2485–9.
Cummins D, Webb G, Shah N, et al. Delayed haemolytic transfusion reactions in patients with sickle cell disease. *Postgrad Med J* 1991;67:689–91.
Epps CH Jr, Bryant DD III, Coles MJ, et al. Osteomyelitis in patients who have sickle cell disease. Diagnosis and management. *J Bone Joint Surg* 1991;73:1281–94.
Fullerton MW, Philippart AI, Sarnaik S, et al. Preoperative exchange transfusion in sickle cell anemia. *J Ped Surg* 1981;16:297–300.
Greenwalt TJ, Zelenski KR. Transfusion support for hemoglobinopathies. *Clin Haematol* 1984;13:151.
Koshy M, Burd L, Wallace D, et al. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. *N Engl J Med* 1988;319:1447–52.
Mintz PD, Williams ME. Cerebrovascular accident during a delayed hemolytic transfusion reaction in a patient with sickle cell anemia. *Ann Clin Lab Sci* 1986;16:214.
Orlina AR, Sosler SD, Koshy M. Problems of chronic transfusion in sickle cell disease. *J Clin Apheresis* 1991;6:234–40.
Piomelli S. Chronic transfusion in patients with sickle cell disease. Implications and problems. *Am J Pediatr Hematol Oncol* 1985;7:51.
Piomelli S, Seaman C, Ackerman K, et al. Planning an exchange transfusion in patients with sickle cell syndromes. *Am J Pediatr Hematol Oncol* 1990;12:268–76.
Rackoff WR, Ohene-Frempong K, Month S, et al. Neurologic events after partial exchange transfusion for priapism in sickle cell disease. *J Pediatr* 1992;120:882–5.
Reisner EG, Kostyu DD, Phillips G, et al. Alloantibody responses in multiply transfused sickle cell patients. *Tissue Antigens* 1987;30:161.
Rosse WF, Gallagher D, Kinney TR, et al. Transfusion and alloimmunization in sickle cell disease. The Cooperative Study of Sickle Cell Disease. *Blood* 1990;76:1431–7.
Schmalzer EA, Lee JO, Brown AK, et al. Viscosity of mixtures of sickle and normal red cells at varying hematocrit levels. Implications for transfusion. *Transfusion* 1987;27:228.
Silliman CC, Peterson VM, Mellman DL, et al. Iron chelation by deferoxamine in sickle cell patients with severe transfusion-induced hemosiderosis: a randomized, double-blind study of the dose-response relationship. *J Lab Clin Med* 1993;122:48–54.
Sosler SD, Jilly BJ, Saporito C, et al. A simple, practical model for reducing alloimmunization in patients with sickle cell disease. *Am J Hematol* 1993;43:103–6.
Talacki CA, Ballas SK. Modified method of exchange transfusion in sickle cell disease. *J Clin Apheresis* 1990;5:183–7.
Vichinsky EP, Earles A, Johnson RA, et al. Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. *N Engl J Med* 1990;322:1617–21.
Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *N Engl J Med* 1995;333(4):206–13.
Wang WC, Kovnar EH, Tonkin IL, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *J Pediatr* 1991;118:377–82.
Wayne AS, Kevy SV, Nathan DG. Transfusion management of sickle cell disease. *Blood* 1993;81:1109–23.

Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease

Serious bacterial infections are a major cause of morbidity and mortality in children with sickle cell disease. Due to the asplenic state and because of altered humoral immunity, infections are more likely to cause morbidity, proliferate, and become resistant in children with sickle cell disease than in other individuals. Septicemia and meningitis due to *S. pneumoniae* are the most common causes of death in early childhood, but enteric organisms are also important pathogens in older individuals with sickle cell disease. While prevention—including early diagnosis, education, immunizations, prophylactic penicillin, and immediate access to medical care—has significantly decreased morbidity and mortality associated with infections in children with sickle cell disease, early and aggressive treatment of infection is a critical element of appropriate medical management.

Because fever is often an important early clinical sign of infection, parents and care providers of children with sickle cell disease are typically instructed to seek prompt medical attention if the child has a temperature of 101.5°F (38.6°C). Consider the febrile child with sickle cell disease septic and treat accordingly until proven otherwise.

The febrile child with sickle cell disease constitutes a *medical emergency*. Begin administering antibiotics immediately.

1. Initial Contacts

- Instruct families and patients to contact their primary care physician or hematologist if the child's temperature is 101.5°F (38.6°C) so the child can be promptly seen and evaluated in a clinic or emergency department (ED).
- As soon as the patient presents at the physician's office, clinic, or ED, evaluate the patient and begin treatment immediately as described below.

Do not delay antibiotic administration.

- To facilitate triage, the referring physician or hematologist should immediately inform the ED staff that the child will be arriving and provide relevant clinical information before the child's presentation.
- If the child presents at the ED without a physician referral, the ED staff should contact the primary care provider or pediatric hematologist responsible for the child's care to obtain background information and ensure appropriate medical management.

2. History

- Duration of current febrile episode
- Associated symptoms, including pain and/or respiratory, gastroenterological, or urinary tract symptoms or complaints
- Current antibiotic usage, including prophylactic antibiotics

- Other current medications
- Allergies
- Pneumococcal vaccine status
- Review of the patient's medical history, focusing on problems related to sickle cell disease and previous infections (such as pneumonia and bacteremia)
- Review of the patient's last comprehensive evaluation and/or baseline information from the patient's hematologist or sickle cell disease treatment center as soon as possible

3. Initial Physical Examination

- Vital signs, including blood pressure and pulse oximetry
- Degree of pallor
- Evidence of sepsis, such as chills, rigors, diminished peripheral perfusion, cool extremities, or localized infection
- Cardiopulmonary status
- Spleen size (compare with the size of the spleen during a steady-state exam, if possible)
- Neurologic exam with attention to meningeal signs

4. Laboratory Evaluation

- Get a stat complete blood count (including WBC differential and platelet count) and reticulocyte count.
- Get a blood culture (if an indwelling central venous catheter is in place, obtain a blood culture from this source).
- If there are respiratory symptoms, neurologic symptoms, extreme pallor, or acute splenic enlargement, get a type and screen/cross match, as a blood transfusion might be required. Request sickle-negative and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for blood types C, E, and Kell is recommended.
- Get a urinalysis and urine culture.
- If there are signs of meningitis, get a cerebrospinal fluid analysis and culture.
- Get other cultures as clinically indicated.

> ***Do not delay antibiotic administration*** **while awaiting laboratory results. (It might be advantageous to obtain blood samples using a butterfly or angiocath that remains in place to expedite administering intravenous antibiotic therapy.)**

- If respiratory tract symptoms are present, perform a chest X-ray. Also consider performing a chest X-ray if there is chest, rib, or upper quadrant abdominal pain; it might indicate a lower lobe infiltrate.

> ***Do not delay antibiotic administration*** **while awaiting X-ray results.**

5. Antibiotic Considerations

- Start appropriate IV antibiotic therapy *immediately***.** Identifying a focus of infection (such as otitis, pharyngitis, or urinary tract infection) does not lessen the urgency of giving parenteral antibiotics.

Table 1
Antibiotic Recommendations

Antibiotic	Children		Adults	
	Dosage	Maximum Dose	Dosage	Maximum Dose
FIRST-LINE CHOICES				
Cefuroxime Common first-line antibiotic with good gram-positive coverage. Not effective against penicillin-resistant *Streptococcus pneumoniae*.	200mg/kg/day divided q 6–8 hours	6g/24 h	6–9g/day IV q 8 h	9g/24 h
Unasyn (Ampicillin/Sulbactam) Recently recommended for its efficacy in treating emerging antibiotic-resistant, gram-positive organisms (penicillin-resistant pneumococcus, *Staphylococcus aureus*) and many gram-negative bacilli (but not *E. coli*). Consider adding an aminoglycoside to Unasyn for suspected gut-associated infection or pyelonephritis.	300–400mg/kg/day (equal to 200mg/kg/day of Ampicillin) IV divided q 6 h	12g/24 h	12g/day IV divided q 6 h	12g/24 h
ALTERNATE CHOICES				
Clindamycin May be substituted for patients with known or suspected cephalosporin or penicillin allergy.	> 1 month old: 25–40mg/kg/day IV divided q 6–8 h	2.7g/24 h	1–2.7g/day IV q 6–8 h	2.7g/24 h
Vancomycin Consider adding Vancomycin (with Cefotaxime) if CNS infection is suspected.	40–50mg/kg/day IV divided q 6–8 hours over 1 h infusion. For suspected CNS disease, dose is 60mg/kg/day.	2g/24 h	2g/day IV q 8 h over 1 h infusion	2g/24 h

Note: Many centers use Ceftriaxone successfully for outpatient management of febrile patients with sickle cell disease. One benefit of this antibiotic is its long action, which facilitates administration by allowing a dosing interval of q 12–24 h. However, Ceftriaxone has been associated with rare cases of fatal intravascular hemolysis when used repeatedly in patients with hemoglobinopathies (JC Bernini et al. Fatal hemolysis induced by Ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995;126:813.

6. Antipyretic Considerations

- Consider antipyretics. It is a common concern that antipyretic therapy might mask fever and make a clinical decision more difficult. However, once the decision has been made to start antibiotic therapy, seriously consider the beneficial effects of antipyretics on the febrile patient with sickle cell disease.
- *Do not use cooling blankets or ice packs for patients with sickle cell disease.*

7. Respiratory Considerations

- See "Evaluation and Initial Management of Acute Chest Syndrome in Children with Sickle Cell Disease."
- The possibility of pneumonia and/or acute chest syndrome must be seriously considered in pediatric patients with sickle cell disease who have fever. Perform a chest X-ray and determine the oxygenation status using pulse oximetry (or ABG) if any of these are present:
  - Complaints of chest pain
  - Toxic appearance
  - Respiratory symptoms
  - Complaints of abdominal pain, which might indicate basilar pneumonia
- *Give supplemental oxygen if the oxygen saturation is less than the patient's baseline.*

8. Decisions About Hospital Admission

- Hospital admission is *strongly recommended* in these situations:
  - Children with sickle cell disease and fever 101.5°F (38.6°C) under 3 years of age (some centers are able to observe for > 4 hours the child's response to treatment without hospitalization after consulting with a pediatric hematologist)
  - Children of any age with sickle cell disease with a temperature of 104°F (40°C)
  - Septic appearance
  - Petechiae
  - Orthostatic changes in blood pressure
  - Indwelling central venous catheter
  - History of past *Streptococcus pneumoniae* bacteremia
  - Evidence of acute complications, including
    - Pulmonary complications (chest pain, increasing oxygen requirements, and/or pulmonary infiltrates that might indicate acute chest syndrome)
    - Aplastic crisis
    - Splenic sequestration
    - Stroke or other altered neurological signs
    - Priapism
- *Strongly consider* hospital admission in these situations:
  - WBC > 30k/µl or < 5k/µl
  - Platelet count < 150k/µl
  - Hemoglobin significantly lower than baseline (if known)
- Also consider hospital admission in these situations:
  - There is no working telephone in the home
  - The family does not have reliable transportation
  - There are other concerns about compliance and follow-up

- Before discharging the patient, see Discharge from the ED with Outpatient Management, below.
- Consider patients with reticulocytopenia and suspicion of Parvovirus infection contagious and admit them following an appropriate isolation protocol.

9. Subspecialty Involvement and Decisions About Transferring the Patient

- Because fever in children with sickle cell disease patients can indicate life-threatening septicemia, consulting a pediatric hematologist with expertise in sickle cell disease is *strongly recommended*.

> ***Do not delay antibiotic administration*** **during evaluation while awaiting transfer of the patient to a sickle cell disease treatment center.**

- *Strongly consider* transferring the patient immediately to a medical center with expertise in sickle cell disease under the following conditions:
  - Chest pain
  - Abdominal pain
  - Pulmonary infiltrates on chest X-ray
  - Hypoxia
  - Toxic appearance
  - Evidence of shock such as hypotension or poor peripheral perfusion
  - Meningeal signs
  - Priapism
  - Altered mental status and/or any neurological changes
  - Acute splenic enlargement
  - Anticipated need for multiple red blood call transfusions or exchange transfusions

10. Discharge from the ED with Outpatient Management

- Consider discharging the patient from the ED to home (no hospital admission) *only* when
  - The patient is not septic.
  - The patient is clinically stable and exhibits none of signs and symptoms for admission outlined above.
  - The patient's stable condition has been established with repeated vital signs in the clinic or ED for at least 4 hours after administering parenteral antibiotics.
  - There is reasonable assurance of adequate family compliance and follow-up as outlined above.
  - The patient's hematologist or primary care provider has approved outpatient management.

For patients discharged directly from the ED to home (not admitted to the hospital), *outpatient management must include a repeat evaluation the following day*. At a minimum, call the patient's family to evaluate the patient's status. If the patient remains febrile at the time of reevaluation, *strongly consider* admitting the patient to the hospital and following ongoing management as outlined in this guideline.

References

Breiman RF, Butler JC, Tenover FC, et al. Emergence of drug-resistant pneumococcal infection in the United States. *JAMA* 1994;271:1831–5.

Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. *N Engl J Med* 1986;314:1593.

Leggiadro RJ. Penicillin- and cephalosporin-resistant Streptococcus pneumoniae and emerging microbial threat. *Pediatrics* 1994;93:500–3.

Overturf GD, Powars D, Baraff LJ. Bacterial meningitis and septicemia in sickle cell disease. *Am J Dis Child* 1977;131:784–7.

Pearson HA, Gallagher D, Chilcote R, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. *Pediatrics* 1985;76:392–7.

Sarnaik S, Kaplan J, Schiffman G, et al. Studies on pneumococcal vaccine alone or mixed with DTP and on pneumococcus type 6B and Haemophilus influenzae type b capsular polysaccharide-tetanus toxoid conjugates in two- to five-year-old children with sickle cell anemia. *Pediatr Infect Dis* 1990;9:181–6 (erratum, *Pediatr Infect Dis* 1990;9:308).

Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453–60.

Wilimas JA, Flynn PM, Harris S, et al. A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med* 1993;329:472–6.

Zarkowsky HS, Gallagher D, Gill FM, et al. Bacteremia in sickle hemoglobinopathies. *J Pediatr* 1986;109:579–85.

Management of Children with Sickle Cell Disease Undergoing General Anesthesia and Surgery

Regardless of the procedure, general anesthesia is associated with a significant risk of postoperative complications, especially acute chest syndrome. To help minimize or eliminate these complications, plan elective procedures carefully and ensure good communication among the hematologist, anesthesiologist, surgeon, and blood bank. Urgent operative procedures require immediate preoperative consultation with a pediatric hematologist who has expertise in sickle cell disease.

1. Preoperative Evaluation

- Obtain a detailed history, documenting the health of the patient. Identify patients with organ damage and coexistent disease; they are at increased risk for perioperative complications. The patients at particularly high risk for perioperative complications—especially acute chest syndrome and vaso-occlusive events—are those with a history of pulmonary disease (reactive airways disease and acute chest syndrome), CNS disease (stroke or neurologic event), recurrent hospitalizations, and those who have been previously heavily transfused.
- Review the transfusion history with attention to
  - Previous reactions to red blood cell transfusions
  - Presence of any red blood cell antibodies
  - Chronic transfusion protocol
- In the preoperative assessment, check for signs of vaso-occlusion, fever, infection, and dehydration.
- In the diagnostic evaluation,
  - Document baseline pulse oximetry.
  - Document baseline complete blood count and reticulocyte count.
  - Type and screen/cross match, as a blood transfusion might be required.
  - If it is clinically indicated, consider renal and liver functions.
  - For patients with acute chest syndrome, asthma, or other pulmonary complications, consider a chest X-ray and pulmonary function tests with bronchodilator response analysis.
  - If it is clinically indicated, consider an electrocardiogram and echocardiogram, especially in patients with chronic iron overload associated with chronic red blood cell transfusions.

2. Preoperative Transfusion

- Request sickle-negative and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for types C, E, and Kell is recommended.
- Before any procedure requiring general anesthesia, strongly consider transfusion therapy for children with hemoglobin SS or S beta thalassemia. Recent data suggest that in most cases, simple transfusion is as effective as partial exchange transfusion. For some patients

(such as those with previous acute chest syndrome or nontransfused neurological complication), serial simple transfusions or exchange transfusions might be indicated.
  - *Simple transfusion.* Transfuse packed red blood cells to increase hemoglobin to 10g/dl.
  - *Partial exchange transfusion or serial simple transfusion.* The measurable goal is to achieve a hemoglobin S of ≤ 30% with a hemoglobin of 10–12g/dl. Keeping the hemoglobin at ≤ 12g/dl avoids complications of hyperviscosity.

Hyperviscosity might contribute to worsening of the clinical condition. To avoid hyperviscosity in transfusion with sickle cell patients, do not transfuse to a hemoglobin > 12g/dl. See "Stroke and Acute Neurologic Event in Children with Sickle Cell Disease."

- Surgery without preoperative transfusion in children with hemoglobin SS and S beta thalassemia may be considered in selected cases for *minor* procedures (e.g., PE tubes and simple dental procedures) with brief anesthetics.
- Preoperative transfusions might not be required for children with hemoglobin SC or S beta thalassemia who do not have a history of recurrent acute chest syndrome or evidence of chronic organ damage.
- With preoperative transfusions, always consider the special circumstances and unique risks associated with each case. Surgical procedures that increase the probability of ischemia or hypoxia deserve special attention. These include cardiothoracic surgery; techniques associated with hypotension, hypothermia, and hyperventilation; and vascular surgery. Use laparoscopic surgery in appropriate settings; it appears to lower the postoperative complications of sickle cell disease.

3. Before Surgery (within 72 hours)
- Get a complete blood count and reticulocyte count.
- If simple transfusion was used, ensure hemoglobin is > 10g/dl.
- After preop transfusions, consider hemoglobin electrophoresis to document hemoglobin S percentage.
- Start intravenous hydration at 1–1½ times maintenance ≥ 12 hours before surgery.
  - Pay strict attention to urinary output and weight.
  - Familiarize the patient with incentive spirometry.

4. Intraoperative
- Make a special effort to avoid hypoxia, hypercarbia, and hyperventilation. Monitor all patients with at least an EKG and have a determination of inspired oxygen concentration by pulse oximetry or blood gas testing. Give the patient a minimum of 50% oxygen combined with the anesthetic agent.
- Depending on the patient's clinical status and the type of surgery, you might need to measure electrolyte and urine output and invasive hemodynamic monitors. (Remember that patients with sickle cell disease generally cannot concentrate urine normally.)
- The operating room should be warm.
- General anesthesia should aim for a normothermic, well-hydrated patient.

- Intraoperative blood salvage techniques (cell savers) are not recommended.
- Avoid surgical tourniquets.

5. Postoperative

- A postoperative hospital stay ≥ 24 hours as clinically indicated is strongly recommended.
- At the discretion of the hematologist, individualize postoperative management after minor procedures (such as PE tubes and simple dental procedures) with brief anesthetics.
- Monitor with pulse oximetry for 18–24 hours to ensure that supplemental oxygen is sufficient to keep saturation > 95%. Postoperatively, administer oxygen until the effects of anesthesia have worn off. Patients who have surgical wounds that interfere with respiration might require an extended use of oxygen. In the recovery room and intensive care unit, continue monitoring by oximetry.
- Administer hydration with oral and intravenous fluids. Avoid excessive hydration, which might precipitate acute chest syndrome. Total hydration (oral, intravenous, and medications) should not exceed a maintenance rate of 1–1½ times. If the patient is dehydrated or if insensible losses are increased, increased fluids may be needed. If signs of fluid overload are present, consider judicious administration of a diuretic such as Lasix.
- To minimize pulmonary complications, incentive spirometry and aggressive respiratory care is necessary. When awake in the daytime, the patient should use the spirometer for at least 10 breaths every 2 hours. To promote rest, wake the sleeping patient during the day only every 4 hours to perform incentive spirometry. At night, wake the patient every 4 hours.
- Administer analgesics (for specific information about management, see "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease"). However, avoid narcotic-induced hypoventilation. Find a delicate balance to provide pain relief and eliminate splinting without causing hypoventilation.
- Until the patient is stable, consider a daily complete blood count including differential, platelet count, and reticulocyte count.
- To prevent constipation, routinely use a stool softener or laxative. In some cases additional laxatives will be required.
- If applicable, continue folic acid and prophylactic antibiotics.
- If other acute concomitant complications associated with sickle cell disease (such as fever, pain, acute splenic sequestration, aplastic crisis, stroke, or priapism) are present, see the guidelines for managing them.

6. Recommended Discharge Criteria

- Adequate oxygenation on room air or back to baseline oxygenation
- Afebrile ≥ 24 hours and no evidence of infection
- Adequate oral intake, including oral medications if needed
- Adequate pain relief (if needed) with oral analgesics

7. Recommended Discharge Considerations, Outpatient Management, and Follow-Up

- Ensure that the patient has ready access to prescription analgesic medication.
- With the surgery and hematology services, coordinate a clear follow-up plan including
  - A return visit to the sickle cell clinic in 2–3 weeks

- A plan for breakthrough pain
- Directions for resuming normal age-appropriate activities

References

Bischoff RJ, Williamson A III, Dalali MJ, et al. Assessment of the use of transfusion therapy perioperatively in patients with sickle cell hemoglobinopathies. *Ann Surg* 1988;207:434–8.

Burrington JD. Elective and emergency surgery in children with sickle cell disease. *Surg Clin North Am* 1976;56:55–71.

Esseltine DW, Baxter M, Bevan JC. Sickle cell states and the anesthesiologist. *Can J Anaesth* 1988;35:385–403.

Fullerton MW, Philippart AI, Sarnaik S, et al. Preoperative exchange transfusion in sickle cell anemia. *J Ped Surg* 1981;16:297–300.

Gibson J. Anesthesia for sickle cell disease and other hemoglobinopathies. *Semin Anesth* 1987;6:27–35.

Homi J. General anesthesia in sickle cell disease. *Br Med J* 1979;1:1599–1601.

Janik J, Seeler RA. Perioperative management of children with sickle hemoglobinopathy. *J Pediatr Surg* 1980;15:117–20.

Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. *Blood* 1995;86(10).

National Institutes of Health. NIH Consensus Development Conference Statement from Perioperative Red Cell Transfusion. June 27–29, 1988; vol. 7, no. 4.

National Institutes of Health, National Heart, Lung and Blood Institute. Surgery and Anesthesia. Chap. 21 in *Management and Therapy of Sickle Cell Disease*, NIH Publication No. 95-2117. 3d ed, rev. December 1995.

Searle JF. Anaesthesia in sickle states. *Anaesthesia* 1973;28:48–58.

Vichinsky EP, Haberkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *N Engl J Med* 1995;333(4):206–13.

Ware R, Filston HC, Schultz WH, et al. Elective cholecystectomy in children with sickle hemoglobinopathies: successful outcome using preoperative transfusion regimen. *Ann Surg* 1988;208:17–35.

Evaluation and Management of Acute Pain In Children with Sickle Cell Disease

For many patients with sickle cell disease, pain is a lifelong experience. This pain, it is suspected, stems from sickled erythrocytes obstructing the blood flow, resulting in ischemic tissue injury. The reduced blood flow causes regional hypoxia and acidosis, which further potentiate the sickling process and can increase the ischemic injury.

Acute pain episodes for patients with sickle cell disease can be recurrent, unpredictable events that vary in frequency, severity, duration, and etiology. They can last as little as 4–6 days or persist for weeks. Episodes can increase in frequency in adolescence and early adulthood. Individuals who experience > 6 episodes per year have a reduced survival rate compared with those who experience less frequent events. While some patients experience frequent acute painful episodes, others develop chronic pain syndromes associated with avascular necrosis, multiple and diffuse bone infarctions, and leg ulcers. Some patients experience constant pain without clear etiology. Pain can be precipitated by hypoxia, infection, fever, acidosis, dehydration, menstruation, obstructive sleep apnea, and exposure to cold. In addition, patients have cited causes including anxiety, depression, and physical exhaustion. But in many instances no precipitating event is identified.

Recurrent pain has an immeasurable negative impact on daily activities, school and work performance, social interactions and relationships, mood, quality of life, and recreation. The psychosocial aspects of chronic pain are complex, and often they are not appropriately addressed. A patient with chronic and recurrent pain must undergo a thorough psychosocial assessment to help define stressors and comorbid conditions such as depression, coping strategies, and support systems.

Managing pain related to sickle cell disease is complex. This document serves as a general guideline for managing pain and is not intended to cover all aspects.

1. Initial Contacts

- General management of pain at home
  - Rest
  - Oral fluids
  - Analgesics using an analgesic ladder approach (refer to tables 2 and 3 for specific dosing recommendations)
    - Step 1: acetaminophen and/or NSAIDs
    - Step 2: acetaminophen or NSAIDs with weak opioid (codeine)
    - Step 3: acetaminophen or NSAIDs with potent opioid

    Standard doses may need to be modified in light of previous narcotic use.

  - Application of heat, such as warm compresses

  - Massage
  - Pleasant distractions such as games, music, and television; relaxation techniques
  - Other supportive measures, both general and specific to the patient
- Referral to clinic or emergency department (ED). If home management is unsuccessful in a reasonable period as judged by the patient and family, or if additional medical complications (such as fever, dehydration, or respiratory symptoms) develop, the patient needs prompt medical attention.

The patient must receive prompt pain relief.

  - To facilitate triage, the referring physician or hematologist should immediately inform the ED staff that the child will be arriving and provide relevant clinical information.
  - If the child presents at the ED without a physician referral, the ED staff should contact the primary care provider or pediatric hematologist responsible for the child's care to obtain background information and ensure appropriate medical management.

Table 1
Common Pain States Associated with Sickle Cell Disease

Pain States			
Acute painful event	• Sudden onset • Pain in any and all parts of body	• Vaso-occlusion • Endothelial damage • Inflammation	• Unpredictable, recurrent • Great variability • All ages
Acute hand-foot syndrome (dactylitis)	• Painful dorsal swelling of hands and feet	• Symmetrical infarcts of metacarpal and metatarsal bones due to obstruction of developing blood vessels	• More common in childhood • Often first manifestation of disease (occurring as early as 6 months old)
Acute inflammation of joints	• Painful swollen joints	• Vaso-occlusion/injury • Inflammation • Infected joints	• Can accompany dactylitis • Acute flare-ups of isolated events • May involve disease of endothelium
Acute chest syndrome	• Chest pain, particularly in rib and substernal area • Chest pain posteriorly (upper back) • Fever, tachypnea, and/or hypoxia	• Pulmonary infiltrates • Can be associated with infarction or infection • Unilateral pain (splinting from atelectasis)	• Can require exchange and be fatal • *Common cause of mortality in children and adults*

Continued on next page

Table 1—*Continued*

Pain States			
Splenic sequestration	• Left upper quadrant pain • Marked pallor • Sudden decrease in hemoglobin concentration • Enlarged spleen	• Blood trapped in the spleen	• Can be catastrophic in young children, with the possibility of circulatory collapse • Insidious in adults • Occurs in older children and adults with Hb SC and Hb S/beta thalassemia
Intrahepatic sickling or hepatic sequestration	• Right upper quadrant pain • Sudden decrease in hemoglobin • Enlarged liver	• Blood pooling in the liver	• Occurs more commonly in adults
Abdominal and intrabdominal pain	• Jaundice	• Cholelithiasis	• Can be the initial manifestation of acute chest syndrome
Priapism	• Painful erection	• Sickling in sinusoids of penis	• Can last from a few hours (acute and brief) to days (acute and prolonged) or be chronic or stuttering (intermittent)
Chronic neuropathic pain	• Pain in back • Spontaneous • Lancinating	• In older adults: disc disease, infections • Collapsed vertebrae • Iron overload neuropathy	• Often not considered in sickle cell disease

Source: Modified from American Pain Society 1999, 4–5.

In general, managing pain is complex and involves an integrated approach encompassing several modalities into the treatment plans, as illustrated in table 2.

Table 2
Sickle Cell Disease Pain Treatment Modalities

Medication	Usual Dose for Children and Adults (≥ 50kg Body Weight)	Usual Dose for Children[a] and Adults[b] (<_50kg Body Weight)
Acetaminophen and over-the-counter NSAIDs		
Acetaminophen[c]	650mg q 4 h PO	10–15mg/kg q 4 h PO
	975–1,000mg q 6 h PO	15–20mg/kg q 4 h PR
Aspirin[d]	650mg q 4 h PO	10–15mg/kg q 4 h PO
	975–1,000mg q 6 h PO	15–20mg/kg q 4 h PR
Ibuprofen	400–800mg q 6 h PO	10mg/kg q 6–8 h[e] PO
Naproxen (Naprosyn)	500 mg initially, then 250mg q 6–8 h PO	5–7mg/kg q 8–12 h PO
Naproxen sodium (Anaprox)	550mg initially, then 275mg q 6–8 h PO	
Prescription NSAIDs		
Choline magnesium trisalicylate (Trilisate)[f]	1,000–1,500mg tid PO	37kg–50 mg/kg/day PO in 2 divided doses; 37kg–2.2 g/day PO in 2 divided doses
Choline salicylate (Arthropan)[f]	870mg q 3–4 h PO	2g/m^2/day PO in 4–6 divided doses
	870–1,305mg q 6 h PO	
Diflunisal (Dolobid)[g]	500mg q 8–12 h[i]	
Ketorolac tromethamine (Toradol)[h]	10mg q 4–6 h PO to a maximum of 40mg/day	
Parenteral NSAIDs		
Ketorolac tromethamine (Toradol)[i, j]	30mg initially, then 15–30mg q 6 h IV, parenteral dose not to exceed 5 days or 120mg/day	0.5mg/kg q 8 h IV

Source: Modified from American Pain Society 1999, 21.

[a]The only medications listed are those the Food and Drug Administration has approved for use as analgesics, but clinical experience has been gained with other medications as well.
[b]Adjust for weight acetaminophen and NSAID dosages for adults weighing < 50kg.
[c]Acetaminophen lacks the peripheral anti-inflammatory and antiplatelet activities of the other NSAIDs.
[d]Aspirin is the standard agent to which other NSAIDs are compared. It can inhibit platelet aggregation for > 1 week and cause bleeding. Aspirin is contraindicated in children with fever or other viral diseases because of its association with Reye's syndrome.
[e]Ibuprofen is not FDA approved for use in children as an over-the-counter medication. It is FDA approved for use in children as a prescription medication for fever; however, some clinicians have had experience in prescribing ibuprofen for pain relief in children.
[f]Can have minimal antiplatelet activity.
[g]Administering with antacids can decrease absorption.
[h]NSAIDs with q 8–12 h dosing might require an initial loading dose of twice the maintenance dose for optimal pain relief in the first 24 hours.
[i]For short-term use only.
[j]Has the same GI toxicities as oral NSAIDs. Its safety and efficacy are not established for use in children.

Table 3
Usual Starting Doses for Opioid Analgesics in Opioid-Naive Patients

	Usual Dose for Adults and Children ≥ 50kg Body Weight[a]		Usual Dose for Adults and Children < 50kg Body Weight[b]	
Medication	Oral	Parenteral	Oral	Parenteral
Short-acting opioid agonists[c]				
Morphine (MSIR)[d]	10–30mg q 3–4 h	5–10mg q 2–4 h	0.3mg/kg q 3–4 h	0.1–0.15mg/kg q 2–4 h
Codeine[e]	15–60mg q 3–6 h	Not available	0.5–1mg/kg q 4–6 h; max dose: 60mg/dose	Not available
Hydromorphone (Dilaudid)[f]	7.5mg q 3–4 h	1.5mg q 3–4 h	0.06–0.08mg/kg q 3–4 h	0.015–0.02mg/kg q 3–4 h
Meperidine (Demerol)[g]	*Not recommended*			
Oxycodone (Roxicodone, OXYIR)	10mg q 4–6 h	Not available		
Combination opioid/NSAID preparations[g]				
Codeine[e] with aspirin or acetaminophen	Codeine component: 60mg q 3–4 h	Not available	Codeine component: 0.5–1mg/kg q 4–6 h; max dose: 60mg/dose	Not available
Hydrocodone (Lorcet, Lortab, Vicodan, others)	10mg q 3–4 h	Not available	0.15–0.2mg/kg q 3–4 h	Not available
Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)	10 q 4–6 h	Not available	0.15–0.2mg/kg q 3–4 h	Not available

Source: Modified from American Pain Society 1999, 31–32, 36.
Note: Published tables vary in the suggested doses that are equianalgesic to morphine. The criterion that must be applied for each patient is clinical response; titrate to clinical responses. Because there is not complete cross-tolerance among drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response.

[a]Caution: Recommended doses do not apply to adult patients with body weight < 50kg.
[b]Caution: Do not use doses listed for patients with body weight < 50kg as initial doses for babies < 6 months old.
[c]Caution: Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics.
[d]For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medication.
[e]Caution: Codeine doses higher than 65mg often are inappropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.
[f]Caution: Chronic administration of meperidine can result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches, myoclonus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.
[g]Caution: These products contain aspirin or acetaminophen. Total daily doses of acetaminophen that exceed 6g can be associated with hepatic toxicity. Aspirin is contraindicated in children in the presence of fever or other viral disease because it is associated with Reye's syndrome.

2. Initial History

- Pain assessment
  - Pain intensity and quality (using age-appropriate instrument)
  - Pain location and impact on function
  - Level of distress
  - Whether the character of the pain is similar to previous sickle cell disease pain
- Probable precipitating factors
- The analgesics already used for this episode
- Previous experience with analgesics and the patient and family's opinion about what best alleviates pain
- Associated symptoms, especially fever, evidence of dehydration, and respiratory distress
- History of acute chest syndrome and asthma
- Allergies to medications
- Problems with constipation due to opioid use
- Problems with pruritis due to opioid use
- Problems with nausea due to opioid use

Pain affecting the chest, abdomen, or back might indicate acute chest syndrome; also consider acute chest syndrome if the patient requires oxygen or has tachypnea or fever. Managing pain in patients with suspected acute chest syndrome is complicated. The goal is to achieve a balance between adequate pain relief to prevent splinting on one hand and avoiding sedation and decreased respiratory effort contributing to hypoxia on the other. See "Evaluation and Initial Management of Acute Chest Syndrome in Children with Sickle Cell Disease."

3. Initial Physical Examination

- Vital signs including pulse oximetry
- Hydration status
- Degree of pallor
- Evidence of infection
- Inspection of sites of pain for swelling and erythema. Pay particular attention to unique sites of swelling that might indicate infection or thrombosis (palpate for venous cords in the leg and arm muscles)
- Cardiopulmonary status

Consider acute chest syndrome if the patient requires oxygen or has tachypnea, fever, or pulmonary findings. See "Evaluation and Initial Management of Acute Chest Syndrome in Children with Sickle Cell Disease."

- Spleen size (compare with baseline exam)
- A genitourinary examination to rule out priapism
- A complete neurologic evaluation, documenting the degree of sedation and orientation

4. Diagnostic Evaluation

- Laboratory studies
  - Complete blood count, including differential, platelet, and reticulocyte count (compare with patient's baseline values).
  - If the patient is febrile, blood cultures (see "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease").
  - If extreme pallor, respiratory or neurologic symptoms, or acute splenic enlargement are present, type and cross match. Request sickle-negative and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for types C, E, and Kell is recommended.
  - If right upper quadrant abdominal pain or epigastric pain is present, consider liver function tests, amylase, lipase, imaging studies, and a surgical consult.
- Radiographic imaging
  - Obtain a chest X-ray if any of the following are present:
    - Chest pain
    - Respiratory signs including oxygen requirement and tachypnea
    - Respiratory symptoms including cough, shortness of breath, and pleuritic pain

    Consider acute chest syndrome if the patient requires oxygen or has tachypnea, fever, or pulmonary findings. See "Evaluation and Initial Management of Acute Chest Syndrome in Children with Sickle Cell Disease."

  - Consider a chest X-ray if either of the following are present:
    - Fever
    - Abdominal symptoms or upper abdominal quadrant pain that might indicate referred symptoms due to a lower lobe pulmonary infiltrate
  - If right upper quadrant abdominal pain or epigastric pain or physical findings are present, consider abdominal imaging, including plain films or ultrasound to investigate for bowel obstruction or cholelithiasis/cholecystitis. Consider a surgical consult and specific laboratory studies.
  - Consider radiologic imaging and an orthopedic consult for localized bone and extremity pain or for physical findings suggestive of osteomyelitis, septic arthritis, or aseptic necrosis.

5. Management

- **Because managing pain and potential complications associated with vaso-occlusive disease in patients with sickle cell disease is complex, consult a physician knowledgeable about sickle cell disease.**
- **When developing a management plan, consider the patient's medical history and unique problems related to previous vaso-occlusive pain events (including previous medication and past response to treatment). Discuss the treatment plan with the patient and family.**
- **Contact and actively involve the patient's primary care provider in the management.**

- Mild to moderate pain (initial medical treatment in the outpatient or ED setting)
  - Hydrate the patient using oral fluids if appropriate. If oral hydration is inappropriate, institute intravenous fluids (5–10cc/kg bolus over 1 h, then maintenance rate). Excessive fluids are not necessary unless the patient is dehydrated.
  - Administer analgesics (oral or parenteral). Refer to tables 2 and 3 for specific dosing recommendations. Choose the analgesic therapy by the site and intensity of pain, type of pain management used at home, and past response to treatment for pain.
  - Discharge considerations
    - If adequate pain relief (observed for a period of at least 2 hours) is achieved, consider giving an oral opioid analgesic (in a potency consistent with the current level of pain intensity) before discharge to test the efficacy of outpatient therapy.
    - If adequate relief is achieved and *no other acute complications are present,* consider discharge on oral analgesics.
    - Ensure that the patient has access to adequate analgesic medication for home use. If not, discharge with at least several doses as well as a prescription for oral pain medications.
    - Continue oral hydration and activity as tolerated.
    - Establish a clear follow-up plan that includes, at a minimum, telephone contact the next day. The patient should also have a follow-up visit with the sickle cell disease clinic.
    - Admit the patient to the hospital if pain persists at an intensity not likely to respond to home management.
    - Consider hospitalization if other medical complications (such as fever, respiratory symptoms, or unusual nature of pain) are present.
- Moderate to severe pain (medical treatment in the hospital setting)

The best approach to managing pain is aggressive analgesic therapy with frequent reassessment of effectiveness.

  - Hydrate with oral and intravenous fluids. Consider giving an intravenous bolus of 5–10cc/kg over 1 hour. Total hydration (oral, intravenous, and medications) should not exceed the 1–1½ times maintenance rate. If the patient is dehydrated or if

insensible losses (such as persistent fever) are increased, increased fluids may be needed. Avoid excessive fluids, which might exacerbate acute chest syndrome.

- Analgesics
  - Refer to tables 2 and 3 for specific dosing recommendations.
  - Determine the analgesic therapy based on site and intensity of pain. Administer a parenteral opioid at a dose consistent with the patient's history and current medical status. See table 4 for equianalgesic doses for opioid analgesics.
  - Dose contingent on time, not PRN.
  - Some patients require a particular opioid because of past adverse effects (such as intractable pruritus, nausea, or seizures).
  - Reassess the patient's pain at 15–30-minute intervals during the first several hours of admission. Reevaluate pain management with the patient at least once a day or more frequently and discuss adjustments and changes in pain management with the patient and family.
  - Adjust the dosing to achieve a balance between relieving pain and avoiding sedation.
  - If the patient requires increasing dosage to control pain, consider alternative techniques such as patient-controlled analgesia.
  - In individual cases and if there is no contraindication (such as gastritis, ulcers, or renal impairment), additional coanalgesics including NSAIDs such as ibuprofen or ketorolac tromethamine (Toradol) might be appropriate. Do not use ketorolac for longer than 5 days. *Do not use ibuprofen with ketorolac*.
  - Avoid parenteral IM shots. In patients with limited access consider a subcutaneous route or an appropriate and durable IV line, such as a peripherally inserted central catheter (PICC).
- Monitoring
  - Monitor vital signs including blood pressure at least every 4 hours or more frequently as indicated.
  - To follow respiratory status, use pulse oxymetry; it also can be useful to monitor for sedation. Keep oxygen saturation at 92% or the patient's baseline value.
  - Assess and record pain intensity at least every 4 hours using an age-appropriate instrument for measuring pain intensity.
  - Record accurate intake and output and daily weight as clinically indicated.
  - If any respiratory symptoms are present, or if there is concern about oversedation while receiving parenteral opioids, consider a cardiorespiratory monitor or continuous pulse oximetry.
- General care
  - Perform incentive spirometry; it is extremely important. During the daytime hours when awake, the patient should use the spirometer for at least 10 breaths every 2 hours. To promote rest, wake the sleeping patient every 4 hours during the day to perform incentive spirometry. During the night, wake the patient every 4 hours.
  - When the patient is able to participate, consider physical therapy.
  - Encourage ambulation and light activity when they are tolerated.
  - Offer heating pads and other comfort measures.
- Other diagnostics during hospital admission
  - Get a complete blood count, including platelet count and reticulocyte count

initially and as clinically indicated. Compare these values with the patient's baseline data.

- Obtain a chest X-ray if any of the following develop after admission:
  - Chest pain
  - Respiratory signs, including oxygen requirement and tachypnea
  - Respiratory symptoms including cough, shortness of breath, and pleuritic pain

Consider acute chest syndrome if the patient requires oxygen or has tachypnea, fever, or pulmonary findings. See "Evaluation and Initial Management of Acute Chest Syndrome in Children with Sickle Cell Disease."

- If the patient is febrile, see "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."
- If parenteral opioids or antibiotics are used as clinically indicated, consider renal (BUN, creatinine) and liver (fractionated bilirubin, ALT, and AST) function tests.
- To rule out cholelithiasis, cholecystitis, or pancreatitis, consider an abdominal ultrasound, liver function tests, and amylase and lipase for severe epigastric or right upper quadrant abdominal pain.
- Type and screen/cross match if the hemoglobin is > 1.5–2.0gm/dl below baseline, or if there are respiratory or neurologic symptoms, or acute splenic enlargement, as a blood transfusion may be required. Request *sickle-negative* and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for blood types C, E, and Kell are recommended.
- Other medications
  - For information on treating side effects associated with opiods, see table 5.
  - Routinely use a stool softener or laxative such as docusate sodium (Colace) to prevent narcotic-induced constipation. In some cases additional laxatives might be required. For opioid-induced pruritis use antihistamines such as diphenhydramine (Benadryl). For opioid-induced nausea, ondansetron hydrochloride (Zofran) or other antiemetic might be useful.
  - If applicable, continue prophylactic folic acid and antibiotics.
- Nonpharmacological interventions. Seriously consider behavioral, psychological, and physical interventions. See figure 1.
- Other considerations. See other specific guidelines for managing concomitant complications such as fever, acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, and priapism.

Table 4
Equianalgesic Doses for Opioid Analgesics in Opioid-Naive Adults and Children, 50kg Body Weight

	Dose[a]	
Medication	Oral	Parenteral
Short-acting opioid agonist		
Morphine (MSIR)[b]	30mg	10mg
Codeine[c]	200mg	120mg
Hydromorphone (Dilaudid)[b]	7.5mg	1.5mg
Meperidine (Demerol)[d] *Not recommended*	300mg	100mg
Oxycodone (Roxicodone, OXY1R)	30mg	Not available
Combination opioid/NSAID preparations[e]		
Codeine (with aspirin or acetaminophen)[c]	180–200mg	Not available
Hydrocodone (Lorcet, Lortab, Vicodan, and others)	30mg	Not available
Oxycodone (Roxicodone; also in Percocet, Percodan, Tylox, and others)	30mg	Not available

Source: Modified from American Pain Society 1999, 35.

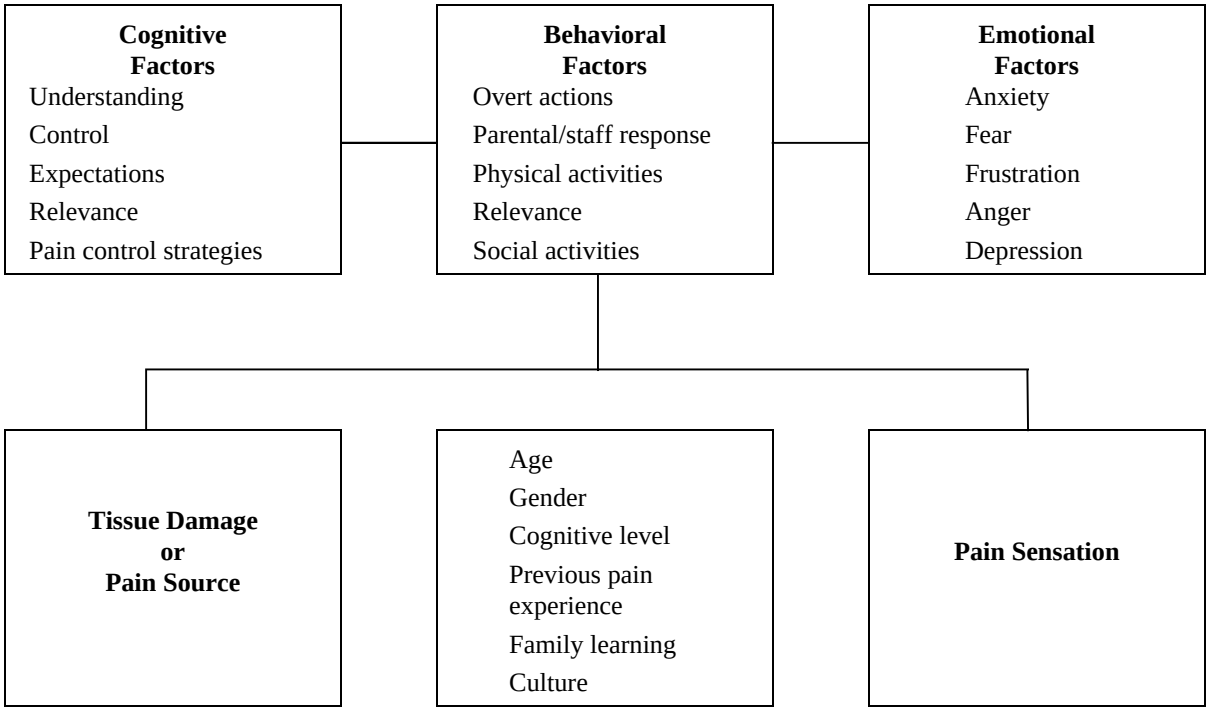
[a]Dose is approximately equal in analgesic effect to morphine sulfate, 10mg parenteral.
[b]For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medication.
[c]Caution: Codeine doses higher than 65mg often are inappropriate because of diminishing incremental analgesia with increasing doses but continually increasing nausea, constipation, and other side effects.
[d]Caution: Chronic administration of meperidine may result in central nervous system stimulation, including agitation, irritability, nervousness, tremors, twitches, myoclonus, or seizures, due to accumulation of the toxic metabolite normeperidine. The risk is much greater for patients with renal or hepatic impairment.
[e]Caution: These products contain aspirin or acetaminophen. Total daily doses of acetaminophen that exceed 6g can be associated with hepatic toxicity. Aspirin is contraindicated for children with fever or other viral disease because of its association with Reye's syndrome.

Table 5
Opioid Side Effects and Their Treatment

Side Effect		
Sedation	Common	Adjust dose of opioid, caffeine, methylphenidate
Nausea	Common	Prochlorperazine, metoclopramide, ondansetron, antihistamines
Pruritis	Common	Diphenhydramine, hydroxyzine
Constipation	Variable	Stool softener, osmotic laxative, diet
Dysphoria	Occasional	Adjust dose of opioid or change opioid
Respiratory depression (respiratory rate < 10 breaths per minute)	Rare	Spirometer, then oxygen, then adjust opioids (naloxone titration if severe)

Source: Adapted from Chapman 1997.

Figure 1
Factors Contributing to the Perception of Pain in Children



Source: Adapted from McGrath and Hillier 1996.

6. Recommended Discharge Criteria

- Wean from analgesics as tolerated *not* by prolonging interval between doses but by decreasing the dose.
- Discuss analgesic changes with the patient and the family before changes.
- If long-acting oral opioids such as morphine sulfate controlled release (MS Contin), oxycodone (Oxycontin), or methadone are scheduled as continuing analgesia after discharge, it may be useful to introduce these while the patient is weaned from the parenteral narcotics.
- Consider a trial of an oral analgesic pain-control regimen such as a combination opioid–NSAID preparation (codeine with aspirin or acetaminophen) while the patient is still in the hospital to ensure that it will relieve pain adequately after discharge. This technique might help avoid recurrence of pain and a possible repeat admission.
- The patient must be able to maintain oral hydration and take oral medications.
- Ensure that the patient has ready access to prescription analgesic medication.

7. Outpatient Management, Discharge Considerations, and Recommended Follow-Up

- Ensure that the patient has access to appropriate analgesic medication for home use.
- Coordinate a clear follow-up plan with the hematology service that includes
  - A return visit to the sickle cell disease clinic in 2–3 weeks
  - A plan for breakthrough pain
  - Directions for resuming normal age-appropriate activities

References

American Pain Society. Treatment of Pain in Sickle Cell Disease, Chap. II, pp. 4–5, and Chap. IV, pp. 21, 31–32, and 36, in *Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease*. August 1999.

Ballas SK. Treatment of pain in adults with sickle cell disease. *Am J Hematol* 1990;34:49–54.

Ballas SK, Delengowski A. Pain measurement in hospitalized adults with sickle cell painful episodes. *Ann Clin Lab Sci* 1993;23:358–61.

Baum FK, Dunn DT, Maude GH, et al. The painful crisis of homozygous sickle cell disease. A study of the risk factors. *Arch Intern Med* 1987;47:1231–4.

Benjamin LJ. Pain in sickle cell disease. In KM Foley, R Payne (eds). *Current therapy of pain.* Ontario, Canada: BC Decker, 1989:90–104.

Benjamin LJ. Sickle cell disease. In M Max, R Portenoy, E Laska (eds). *Advances in Pain Research and Therapy.* Vol. 18. New York, New York: Raven Press, 1991.

CR Chapman. "Reaching the Optimal Balance: Treating Pain While Maintaining Opioid Side Effects. Raising the Standard of Care in Cancer Pain Management." Symposium presented at the American Cancer Society 16th Annual Scientific Meeting, 1997, 13–20.

Cole TB, Sprinkle RH, Smith SJ, et al. Intravenous narcotic therapy for children with severe sickle cell pain crisis. *Am J Dis Child* 1986;140:1255–9.

Foley MK, Inturrisi EC. Analgesic drug therapy in cancer pain: principles and practice. *Med Clin North Am* 1987;71:207–32.

Gaukroger PB. Patient-controlled analgesia in children. In NL Schechter, CB Berde, M Yaster (eds). *Pain in Infants, Children, and Adolescents.* Baltimore, Maryland: Williams & Wilkins, 1993:203–11.

Gil KM. Coping with sickle cell disease pain. *Ann Behav Med* 1989;11:49–57.

Karko RF, Foley KM, Grabinsky PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983;13:180–5.

PA McGrath, LM Hillier. "Controlling Children's Pain." In RJ Gathchel, DC Turk (eds.). *Psychological Approaches to Pain Management.* New York, New York: Guilford Press, 1996.

National Institutes of Health, National Heart, Lung and Blood Institute. Painful Events. Chap. 7 in *Management and Therapy of Sickle Cell Disease*, NIH Publication No. 95-2117. 3d ed, rev. December 1995.

Payne R. Pain management in sickle cell disease: rationale and techniques. *Ann NY Acad Sci* 1989;565:189–206.

Perlin E, Finke H, Castro O, et al. Infusional/patient-controlled analgesia in sickle-cell vaso-occlusive crises. *Pain Clinic* 1993;6:113–9.

Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. *N Engl J Med* 1989;320:1234–8.

Shapiro BS. The management of pain in sickle cell disease. *Pediatr Clin North Am* 1989;36:1029–45.

U.S. Department of Health and Human Services, Public Health Service, Acute Pain Management Guideline Panel. *Acute Pain Management: Operative or Medical Procedures and Trauma.* AHCPR publication no. 92-0032. Rockville, Maryland: Agency for Health Care Policy and Research, 1992.

White PF. Use of patient-controlled analgesia for management of acute pain. *JAMA* 1988;259:243–7.
Yaster M, Tobin JR, Billett C, et al. Epidural analgesia in the management of severe vaso-occlusive sickle cell crisis. *Pediatrics* 1994;93:310–5.

Evaluation and Management of Priapism In Children with Sickle Cell Disease

Priapism is a sustained, unwanted, and painful erection usually unrelated to sexual activity. It is a hematologic and urologic emergency requiring urgent intervention to avoid irreversible ischemic penile injury, fibrosis, and impotence. While several nonsurgical and surgical therapeutic interventions are used, none are predictably effective in relieving priapism or preventing impotence. Obtain a consultation with a urologist, preferably one who has experience treating sickle cell patients with priapism.

- Incidence ranges from 2–6% in children in patients as young as 2 or 3 years old.
- By adulthood, as many as 46% of patients have experienced priapism.
- Two clinical presentations are seen:
  - Stuttering (multiple, short episodes)
  - Severe, prolonged (> 24 hours)

1. Initial Contacts

- Instruct families and patients to contact their primary care physician or hematologist if the child's episode of priapism lasts > 1 hour.
- As soon as the patient presents at the physician's office, clinic, or ED, evaluate the patient and begin treatment immediately as described below.
- To facilitate triage, the referring physician or hematologist should immediately inform the ED staff that the child will be arriving and provide relevant clinical information before the child's presentation.
- If the child presents at the ED without a physician referral, the ED staff should contact the primary care provider or pediatric hematologist responsible for the child's care to obtain background information and ensure appropriate medical management.

2. Initial History

- Duration of symptoms
- History of priapism
- Recent history of transfusion
- Reported history of trauma
- Associated symptoms including fever, evidence of dehydration, and urinary retention
- Pain assessment
  - Pain intensity and quality (using an age-appropriate instrument)
  - Analgesic use
- List of current medications
- Problems with pruritis due to previous opioid use
- Problems with nausea due to previous opioid use

3. Initial Physical Examination

- Vital signs
- Hydration status
- Genitourinary status
  - Presence of bladder distention
  - Turgor of corpora cavernosa
  - Flaccidity of corpora spongiossa

4. Diagnostic Evaluation

- Get a complete blood count with differential, platelet count, and reticulocyte count.
- Get a blood culture if febrile. See "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."
- Get a type and screen/cross match if transfusion is anticipated. Request *sickle-negative* and leukocyte-depleted blood. If available, minor-antigen matched blood or blood negative for blood types C, E, and Kell is recommended. Also consider quantitative hemoglobin electrophoresis if transfusion is anticipated.
- Consider obtaining a color doppler of penile vessels or a radio nucliotide scan.

5. Management

- Initial interventions in the outpatient or ED setting
  - Hydration. Provide intravenous fluids 5–10cc/kg bolus over 1 h, then intravenous fluids at 1–1½ times maintenance rate. Excessive fluids are not necessary unless the patient is dehydrated.
  - Analgesics. Provide parenteral narcotics to relieve pain. For specific dosing recommendations, see "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease," tables 2 and 3. Determine the choice of analgesic therapy by the intensity of pain, type of pain management used at home, and past response to treatment for pain.
  - If needed, insert a Foley catheter to promote bladder emptying.
- Ongoing observation and management
  - Consider simple transfusion as a means of increasing blood flow to areas of poor circulation. Request *sickle-negative* and leukocyte-depleted blood. If available, minor-antigen matched blood or blood negative for blood types C, E, and Kell is recommended.

    Hyperviscosity might contribute to worsening of the clinical condition. To avoid hyperviscosity in transfusion with sickle cell patients, do not transfuse to a hemoglobin > 12g/dl. See "Stroke and Acute Neurologic Event in Children with Sickle Cell Disease."

  - Consider exchange transfusion to reduce the percentage of hemoglobin S if the clinical condition does not show improvement within 24 hours of simple transfusion.
- Surgical intervention. If there is no clinical improvement after hydration, analgesic, or transfusion therapy, or if the clinical condition worsens, get a consultation from an experienced urologist. Consider the following procedures:

  - Penile aspiration and irrigation with dilute alpha adrenergic agonists: 1:1 million epinephrine (1 milliliter 1:1,000 epinephrine in 1 liter saline).
  - If penile aspiration is unsuccessful, a spongiosum-caverosum shunt (Winter procedure).
- Other interventions
  - In patients with recurrent or stutter episodes, use of oral pseudoephedrine, cavernous self-administration of epinephrine, or etilefrine (not available in the United States) are suggested.
  - In chronic refractory cases, use of the gonadotrophin-releasing hormone analogue Lupron has also been suggested**.**

6. Recommended Discharge Criteria

- The patient is clinically stable, as evidenced by the ability to maintain oral hydration, take oral medications, and void spontaneously.
- The patient has ready access to prescription analgesic medication for home use.
- A clear follow-up plan has been coordinated with hematology or urology services that includes a return visit to the sickle cell disease clinic in 2–3 weeks and consultation with a urologist.

7. Recommended Discharge Follow-Up Care

- Tell families and patients that it might take days or weeks to resolve penile erection and return to normal flaccidity.
- Tell families and patients that if the clinical condition worsens or a new painful erection that lasts > 1 hour develops, they should notify the primary care physician or hematologist.
- Tell families and patients that psychological counseling might be indicated to address issues of sexual dysfunction.
- Instruct patients to increase oral intake and to avoid urinary retention by emptying the bladder frequently.
- Tell families and patients that warm baths might increase comfort and to *avoid cold compresses at all times.*

References

Bertram RA, Webster GD, Carson CC. Priapism: etiology, treatment, and results in a series of 35 presentations. *Urology* 1985;26:229–32.

Emond AM, Holman R, Hayes RJ, et al. Priapism and impotence in homozygous sickle cell disease. *Arch Intern Med* 1980;140(11):143–7.

Hamre MR, Harmon EP, Kirkpatrick DV, et al. Priapism as a complication of sickle cell disease. *J Urol* 1991;145:1–5.

Hashmat AI, Das S. *The Penis.* Philadelphia, Pennsylvania: Lea and Febiger, 1993.

Hashmat AI, Samanthi R, Singh I, et al. 99m Tc penile scan: an investigative modality in priapism. *Urol Radiol* 1989;11:58–60.

Noe HN, Wilimas J, Jerkins GR. Surgical management of priapism in children with sickle cell anemia. *J Urol* 1981;126(6):770–1.

Rackoff WR, Ohene-Frempong K, Month S, et al. Neurologic events after partial exchange transfusion for priapism in sickle cell disease. *J Pediatr* 1992;120:882–5.
Sharpsteen JR Jr, Powars D, Johnson C, et al. Multisystem damage associated with tricor-poral priapism in sickle cell disease. *Am J Med* 1993;94:289–95.
Winter CC. Priapism cured by creation of fistule between glans penis and corpora cavernosa. *J Urol* 1980;423:595–6.

Evaluation and Management of Acute Splenic Sequestration In Children with Sickle Cell Disease

Acute splenic sequestration is an acute illness characterized by an increase in spleen size and a decrease in hemoglobin of ≥ 2g/dl below the patient's baseline hemoglobin value. Although life-threatening events are more common in patients younger than 3 years of age, splenic sequestration can occur at any age in patients with sickle cell disease. Mild to moderate thrombocytopenia is often present, and it can precede a significant decrease in hemoglobin. Reticulocytosis equal to or greater than baseline is usually present. If the reticulocyte count is decreased, consider coexistent aplastic crisis. Acute splenic sequestration can have a spectrum of presentations from circulatory collapse to an incidental finding during a routine visit.

1. Initial Contacts

- Tell families and patients to call their primary care physician or hematologist if the child's spleen is larger than usual or if the child is experiencing abdominal discomfort, general irritability, increased pallor, or lethargy.
- If the child is referred to an emergency department (ED), the referring physician should immediately inform the ED that the child will be arriving and provide relevant clinical information before the child's presentation. Confirm baseline spleen size, hemoglobin, and reticulocyte count, if known.
- If the child presents at the ED without physician referral, the ED staff should immediately contact the primary care provider and the pediatric hematologist responsible for the child's care to ensure appropriate medical management.
- After presentation, evaluate the patient immediately. If the child is markedly pale, tachypneic, or lethargic, the staff should triage as an emergency and initiate treatment for hypovolemic shock.

2. History

- Duration of abdominal symptoms such as pain and spleen enlargement
- Any associated symptoms such as pallor, fever, or lethargy
- Recent transfusions and transfusion reaction
- Previous spleen size
- Baseline complete blood count and reticulocyte count
- Episodes of splenic sequestration

3. Initial Physical Examination

- Documentation of palpation of liver and spleen size
- Vital signs, including blood pressure and oxygen saturation
- Degree of pallor
- Hypovolemic shock
- Cardiopulmonary status
- Neurological status

4. Initial Laboratory Evaluation

- Stat complete blood count with differential, platelet count, and reticulocyte count.
- Stat type and screen/cross match for packed red blood cells. Consider using O-negative blood in the case of cardiovascular instability. If time permits, use minor-antigen-matched, sickle-negative, and leukocyte-depleted packed red blood cells.
- If the patient is febrile, blood culture, urinalysis, and urine culture.
- If the patient is febrile or if any signs or symptoms of respiratory illness are present, consider a chest X-ray (see "Evaluation and Initial Management of Febrile Illness $T \geq 101.5°F$ (38.6°C) in Children with Sickle Cell Disease").

Children who need to be admitted for acute splenic sequestration should go to a hospital where physicians and nurses with expertise in pediatric sickle cell disease and critical care can direct and participate in their care.

5. Management

- Monitoring
  - Consider ICU admission for signs of cardiovascular compromise.
  - Vital signs q 2 h until stable, then q 4 h.
  - CR monitor.
  - Continuous pulse oximetry.
  - Record I + 0 and daily weight.
  - Serial exams (initially q 2–4 h) to reassess cardiovascular status and spleen size.
  - Repeat complete blood count as frequently as every 2 hours, depending on severity of anemia, rate of fall in hemoglobin level, platelet count, and changes in spleen size.
- General care
  - Establish secure venous access.
  - For patients with hemodynamic compromise, give fluid resuscitation while awaiting emergent red cell transfusion.
  - Give hemodynamically stable patients maintenance fluids. Adjust fluid intake for increased insensible losses, such as persistent fever.
- Medication/treatment

If hemoglobin is < 4–5g/dl or for impending cardiovascular compromise, transfuse PRBCs at 10cc/kg. These patients are typically hypovolemic, and rapid transfusion is often indicated.

  - To maintain cardiovascular stability, serial transfusions might be needed.
  - With recovery, autotransfusion can occur as the spleen decreases in size, resulting in a hemoglobin value higher than expected. Therefore, the goal of transfusion should not exceed 8g/dl of hemoglobin.
  - In severe cases with cardiac failure, exchange transfusion might be necessary.

- In patients with extremely low hemoglobin values or cardiovascular instability, administer 100% oxygen by nonrebreathable mask until the anemia is improved and the patient is stable.
- Administer acetaminophen 15mg/kg po q 4 h and/or ibuprofen 10mg/kg po q 6 h for any fever or mild pain. (Hyperthermia can exacerbate cardiovascular compromise with severe anemia.)

6. Recommended Discharge Criteria

- Stable hemoglobin and spleen size for 24 hours
- Taking oral fluids well and able to take oral medications such as prophylactic penicillin if applicable
- Afebrile for 24 hours
- A clear follow-up plan has been arranged for a return visit to the sickle cell clinic within 2 weeks

7. Recommended Discharge Follow-Up

- Confirm that the patient has received pneumococcal and *H. influenzae* vaccines.
- If a splenectomy is planned, consider a meningococcal vaccine.

Children who have had 1 episode of acute splenic sequestration are at high risk for recurrence. They must follow up with pediatric hematology for ongoing consideration of the need for surgical splenectomy and chronic transfusions.

- Reeducate the parents and other caregivers about assessing spleen size and the need to seek immediate medical attention if they notice increased pallor, abdominal pain or enlargement, or rapid splenic enlargement.

References

Emond AM, Collis R, Darvill D, et al. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. *J Pediatr* 1985;107:201.

Kinney TR, Ware RE, Schultz WH, et al. Long-term management of splenic sequestration in children with sickle cell disease. *J Pediatr* 1990;117:194.

Pattison JR, Jones SE, Hodgson J, et al. Parvovirus infections and hypoplastic crises in sickle cell anemia. *Lancet* 1981;1:644.

Seeler RA, Shwiaki MZ. Acute splenic sequestration crises in young children with sickle cell anemia. *Clin Pediatr* 1972;11:701.

Serjeant GR, Serjeant BE, Thomas PW, et al. Human parvovirus infection in homozygous sickle cell disease. *Lancet* 1993;341:1237–40.

Topley AM, Rogers DW, Stevens MCG, et al. Acute splenic sequestration and hyper-splenism in the first five years in homozygous sickle cell disease. *Arch Dis Child* 1981;56:765.

Stroke and Acute Neurologic Event In Children with Sickle Cell Disease

Clinically evident stroke is a devastating complication of sickle cell disease that affects 6–12% of patients. In children under 10 years of age, the most common cause of stroke is cerebral infarction. Ischemic stroke typically presents with signs and symptoms of hemiparesis or monoparesis, hemianesthesia, visual field deficits, aphasia, cranial nerve palsies, or acute change in behavior. Although occasionally recovery is complete, intellectual, motor, and sensory impairments are typically sequelae. With advancing age, intracranial hemorrhage becomes increasingly more common. In hemorrhagic stroke, more generalized phenomena such as coma, headache, and seizures occur.

Recurrent stroke causes progressively greater impairment and increased likelihood of mortality. *Completed stroke* signifies a fixed neurologic deficit, while *stroke in progression* implies worsening of the neurologic deficit or the appearance of new focal abnormalities while the patient is under observation.

Nonfocal complaints such as dizziness, headache, and fainting do not in themselves represent cerebral vascular disease, but they should be investigated carefully. A transient ischemic attack (TIA) is a focal neurologic deficit persisting < 48 hours (< 24 hours for internal carotid, anterior, or middle cerebral arteries and < 48 hours for vertebral or basilar arteries) that follows a vascular distribution. Typically, there is no clinically apparent residual deficit from a TIA, though newer imaging modalities such as MRI and positron emission tomography (PET) have identified ischemic brain lesions in both the gray and white matter of some patients. TIA often is a harbinger of subsequent stroke.

Infarction usually occurs in a segmental pattern that suggests damage to the large cerebral arteries. The most common abnormalities found on arteriography or magnetic resonance angiography (MRA) are marked narrowing or complete occlusion of the anterior cerebral arteries (ACA) and middle cerebral arteries (MCA). Multiple, bilateral vessel involvement is usual, even in patients who have unilateral neurologic signs. Vessel narrowing results from intimal and medial proliferation, which in turn is thought to result from endothelial damage from sickled red blood cells. The damaged, irregular endothelium can serve as a nidus for the adhesion of platelets and sickle cells, thereby resulting in thrombus formation. The stroke event occurs when narrowing is severe enough to compromise distal flow or when the thrombus dislodges and causes distal embolization. Transient neurologic symptoms can result from a vessel spasm. Intracranial hemorrhage can be intracerebral or subarachnoid and can result from rupture of an aneurysm of the circle of Willis. Intracerebral hemorrhage can also occur years later in patients who had previous cerebral infarction resulting from a rupture of fragile collateral vessels (moyamoya).

Transcranial Doppler (TCD) studies or ultrasonography of the large cerebral vessels can help identify a narrowing of the MCA or ACA, a reliable indicator that a patient is at risk of stroke. These studies are useful noninvasive screening techniques, but an acute neurologic emergency requires diagnostic measures such as MRI and MRA that provide more definitive imaging.

- **Acute neurologic changes in a child with sickle cell disease constitute a *medical emergency*.**
- **Consult a pediatric hematologist with expertise in sickle cell disease about acute management.**
- **Appropriately managing stroke in a patient with sickle cell disease is uniquely different from managing other neurovascular emergencies. Do not institute standard protocols for treating ischemic stroke such as using antithrombotic agents. They are contraindicated in hemorrhagic strokes.**
- **If there is suspicion that the patient has suffered a stroke or other neurovascular event, strongly consider immediate transfer to a medical center with expertise in sickle cell disease.**

1. Initial Contacts

- Tell families and patients to contact their primary care physician or hematologist if there are any changes in the child's neurologic state (signs and symptoms include numbness, inability to use an extremity, confusion, somnolence, seizures, and severe headache) so the child can be promptly seen and evaluated in a clinic or emergency department (ED).
- As soon as the patient presents at the physician's office, clinic, or ED, evaluate the patient and begin treatment immediately as described below.
- To facilitate the triage of the patient, the referring physician or hematologist should immediately inform the ED staff that the child will be arriving and provide relevant clinical information before the child's presentation.
- If the child presents at the ED without a physician referral, the ED staff should contact the primary care provider or pediatric hematologist responsible for the child's care to obtain background information and ensure appropriate medical management.

2. History

- Ask detailed questions focusing on changes in the child's neurologic signs and symptoms.
  - Signs and symptoms can include overt changes such as hemiparesis or monoparesis, hemianesthesia, syncopal episodes, seizures, gait changes, visual field deficits, aphasia, cranial nerve palsies, headache, and acute change in behavior.
  - Because other symptoms can be subtle, obtain a specific history including changes in mood and activity level and muscle weakness.
  - Ask about any recent changes in school behavior, especially a decrease or change in skills and learning.
  - Note any transient changes that are now resolved.
- Associated symptoms, including pain and fever.
- Current medications, including all medications used for pain management.
- Possibility of ingesting toxins or illicit drugs.
- Allergies.
- Medical history focusing on problems related to sickle cell disease.
- As soon as possible, review the patient's last comprehensive evaluation and baseline information from the patient's hematologist or sickle cell disease treatment center.

3. Initial Physical Examination

- Vital signs, including blood pressure and pulse oximetry, as indicated.
- *A complete neurological evaluation is essential.*
- Cardiopulmonary status.

4. Diagnostic Evaluation

- Laboratory
  - Complete blood count (including WBC differential and platelet count) and reticulocyte count. Compare these with patient's baseline values.
  - Type and screen/cross match, as a blood transfusion or exchange transfusion might be required. Request *sickle-negative* and leukocyte-depleted blood. If available, minor-antigen-matched blood or blood negative for blood types C, E, and Kell is recommended. Before transfusion, send blood for red blood cell phenotype, as this baseline information might be important later if the patient is placed on a chronic transfusion protocol. Do not delay transfusion therapy while awaiting these results.
  - If the patient is febrile or has a recent history of fever, blood and urine culture.
  - Only if clinically indicated, consider a lumbar puncture for examination and culture of cerebral spinal fluid. Do a lumbar puncture only if a computerized tomographic (CT) scan or MRI reveals no evidence of increased intracranial pressure.
  - For baseline information before transfusion, consider hemoglobin electrophoresis.
  - If the patient is severely ill or encephalopathic, consider a chemistry profile to assess renal (BUN and Creatinine) and liver (fractionated bilirubin, ALT, and AST) function.
  - Consider a screening coagulation profile.
  - If clinically indicated, consider a toxicology screen.
- Imaging
  - As an emergency diagnostic procedure, perform a high-resolution CT scan *without* contrast. The CT scan might be normal at the onset in cerebral infarction, but it is helpful in ruling out bleeding, abscess, tumor, and other abnormalities. A CT scan 2 to 7 days later typically is able to demonstrate the area of infarction.
  - To document the extent of cerebral damage and to evaluate and visualize major intracerebral vessels, do an MRI or MRA once the patient is clinically stable. However, MRI or MRA scanning requires more time at the imaging center than CT scanning does, and high-resolution equipment (1.5 tesla or more) is required.
  - Arteriography is not necessary to confirm cerebral infarction demonstrated by CT scan, MRI, or MRA, but it can be helpful in clarifying the diagnosis in the rare symptomatic (hemiparesis) patient with normal CT or MRI scans. Using hyperosmolar contrast material makes arteriography potentially hazardous in patients with sickle cell disease.
  - The prognostic value of newer techniques such as PET or metabolic MRI is under intensive investigation. Data suggest that abnormalities on metabolic MRI scans or PET scans in sickle cell disease patients who do not have overt neurologic deficits might be useful in identifying patients at risk for progression of the cerebral vasculopathy and future strokes.
  - TCD is not indicated for evaluating an acute neurological event.

4. Management

- **All patients suspected of having a stroke or acute neurologic event must be admitted to the hospital. Depending on the clinical situation, the intensive care unit may be required for appropriate monitoring of a rapidly changing clinical state.**
- **Because stroke is a life-threatening emergency, it is strongly recommended that a pediatric hematologist with expertise in sickle cell disease be consulted.**
- **Strongly consider immediate transfer to a medical center with expertise in sickle cell disease if a stroke or acute neurologic event is suspected.**

- Red blood cell transfusion
  - The main objective of an emergent red blood cell transfusion is to rapidly reduce the level of the hemoglobin S and therefore decrease further tissue damage associated with ongoing vaso-occlusion of the cerebral vessels. The measurable goal is to achieve a level of hemoglobin S < 30% with a hemoglobin of 10–12g/dl. Keeping the hemoglobin ≤ 12g/dl avoids complications of hyperviscosity.
  - One effective method of decreasing the level of hemoglobin S is a partial exchange transfusion (or erythrocytapheresis).
  - A straight transfusion using packed red blood cells may be considered as an alternative to partial exchange transfusion for stable patients with hemoglobin < 6–7g/dl.
  - Institute a chronic transfusion program before discharge (see Recommended Discharge Criteria, below).

Rapid increases in the hemoglobin level can result in hyperviscosity that might contribute to worsening of the clinical condition.

- Hydration
  - Total intravenous hydration should not exceed a 1–1½ times maintenance rate. Increased fluids might be needed if patient is dehydrated or if insensible losses such as persistent fever are increased.
  - If signs of fluid overload are present, consider judicious administration of a diuretic such as Lasix.
- Monitoring and supportive care
  - For the patient with acute occlusive stroke, rapid evaluation and careful monitoring are essential. Admit patients to an intensive care unit. *Perform* vital signs and neurological evaluation frequently during the first 24 hours of hospitalization.
  - Treat increased intracranial pressure promptly with pharmacological agents. Assisted ventilation might be necessary, but avoid hyperventilation therapy.
  - Involve a neurologist and/or neurosurgeon.
  - Seizures are common during acute infarction and hemorrhage and require anticonvulsant therapy.
  - Monitor for hypertension and control blood pressure.

  - Monitor with continuous pulse oximetry and a cardio-respiratory monitor.
  - If the patient is in pain, assess and record pain intensity at least every 4 hours using an age-appropriate pain intensity measurement instrument. See "Evaluation and Management of Acute Pain in Children with Sickle Cell Disease" for specific information about analgesic management.
  - If the patient is febrile, see "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease" for specific information about antibiotic dosing.
  - Record accurate intake and output and daily weight as clinically indicated.
- Oxygen therapy
  - Oxygen therapy is indicated for hypoxemia, tachycardia, and tachypnea.
  - Monitor continuous oxygen saturation and consider measuring arterial blood gases if clinically indicated.
  - Provide oxygen therapy to maintain oxygen saturation ≥ 94% (or enough to keep at baseline oxygen saturation percentage). Adjust oxygen delivery as needed for the patient's comfort and cardiovascular stability.
- General care and rehabilitation
  - Begin physical and rehabilitative therapy when the patient is clinically stable and able to participate.
  - Offer psychological evaluation and individual or family counseling if appropriate.
- Other diagnostics during hospital admission
  - Perform a complete blood count, including platelet and reticulocyte count, initially and as clinically indicated following initial transfusion therapy during the hospital course.
  - Document post-transfusion hemoglobin S level < 30%.
  - Consider performing follow-up neuro-imaging studies to document stabilization of lesion.
  - If the patient is febrile, see "Evaluation and Initial Management of Febrile Illness T ≥ 101.5°F (38.6°C) in Children with Sickle Cell Disease."
  - Consider renal (BUN, Creatinine) and liver (fractionated bilirubin, ALT, and AST) function tests as clinically indicated.
- Other medications
  - Consider a stool softener such as docusate sodium (Colace) for constipation if indicated. Additional laxatives might be required in some cases.
  - If applicable, continue prophylactic folic acid and prophylactic antibiotics.
- Other considerations
  - Refer to other specific guidelines for managing acute concomitant complications associated with sickle cell disease, such as fever, pain, acute splenic sequestration, aplastic crisis, stroke, and priapism, if present.
  - For patients who experience a TIA, perform a CT scan or MRI/MRA. Patients with persistent or severe headaches, syncopal episodes, or seizures require thorough evaluations, often by a neurologist, and might need neurologic imaging.

5. Recommended Discharge Criteria

- Clinically and neurologically stable for at least 24 hours after transfusion therapy
- Afebrile ≥ 24 hours and no evidence of infection
- Adequate oral intake, including oral medications if needed
- Adequate pain relief (if needed) with oral analgesics

6. Outpatient Management, Discharge Considerations, and Recommended Follow-Up

- Preventing recurrent vaso-occlusive strokes
  - Vaso-occlusive strokes recur in at least two-thirds of patients unless they are placed on a chronic program. Transfusions of packed red blood cells at regular intervals to keep the level of hemoglobin S level < 30% are effective in minimizing a recurrence of cerebral infarction in children.
  - The optimal duration of transfusion therapy is not known. For now, the standard of care is to continue transfusion indefinitely. The risk of recurrence in untransfused children is greatest in the first 3 years after the initial event. Many centers transfuse patients for years but modify the intensity of transfusions to reduce the rate of iron accumulation. Centers that transfuse patients for long periods use iron-chelating agents (deferoxamine mesylate) to decrease iron overload.
- Comprehensive rehabilitative services
  - In addition to transfusions, it is important to provide comprehensive rehabilitation services to the patient. These services might include physical therapy, occupational therapy, and speech therapy. Although many children may exhibit remarkable recovery from strokes, acquired learning difficulties can result. Perform a detailed assessment of intellectual function to determine if the child would benefit from special help with academic work. When the patient is clinically stable, perform a formal neuropsychological evaluation, and if appropriate, consider an individualized educational program.
  - If appropriate, encourage ongoing psychological individual and family counseling.
  - Ongoing follow-up with neurology is sometimes recommended. Should neurologic symptoms develop in adequately transfused patients, repeat imaging studies are warranted. Prognosis for long-term neurologic function and independent self-sufficient adult life is guarded.
- Other considerations
  - One alternative to chronic transfusion therapy is bone marrow transplantation.
  - The role of hydroxyurea therapy as an alternative to chronic transfusion therapy for these patients is unclear at present.
  - Although aspirin or coumadin therapy has been effective in decreasing the risk of recurrent stroke in adult patients with normal hemoglobin (AA) or those who have experienced a previous TIA, the efficacy of this therapy in central nervous system disease in patients with sickle cell disease has not been established.
  - Consider evaluation for hypercoaguability under appropriate circumstances following a consultation with a pediatric hematologist.

Transcranial Doppler Ultrasonography Screening In Children with Sickle Cell Disease

Background

Transcranial Doppler (TCD) ultrasonography is a sensitive, noninvasive method for assessing blood flow velocities in the large intracranial vessels of the circle of Willis. Blood flow velocity is directly related to cerebral blood flow and inversely related to the diameter of the vessel. Focal stenosis can be identified by the increased velocity resulting from reduced arterial diameter. In a series of studies, TCD has been used to establish normal ranges in flow velocity (in normal children and in children with sickle cell disease-SCD-SS); to compare with angiographic, MRI, and MRA findings; and to establish flow velocities predictive of infarctive stroke. In a recent controlled study, chronic transfusion therapy to maintain hemoglobin S < 30% was shown to reduce the incidence of first stroke in SCD-SS children with abnormal TCD.

The clinical implications of these studies are:

- Children with SCD-SS should be screened with TCD to detect those at risk for infarctive stroke.
- Children with mean TCD velocities > 200cm/sec in the internal carotid artery or middle cerebral artery should be offered chronic transfusion therapy to maintain hemoglobin S < 30%.
- Clinical management of children with ICA or MCA velocities 170–200cm/sec is unclear.

These values were established in a nationwide study using standardized nonimaging (blind) equipment with strict quality control. Exercise extreme caution in using these ranges to derive values from imaging/color doppler equipment.

TCD Screening

All children 2–18 years of age with SCD-SS or SCD-S beta thalassemia should have at a minimum 1 TCD study per year.

Mean TCD velocities in the ICA or MCA will be interpreted as follows:

- < 170cm/sec = low risk (“normal”)
- 170–200cm/sec = intermediate risk abnormal (“conditional”)
- > 200cm/sec = high risk (“abnormal”)

Note: In normal children 5–15 years old, mean TCD velocity in MCA is 79 +/– 13.

Recommendations for clinical management of patients with abnormal TCD

- To be considered for clinical management decisions, all abnormal TCD results must be repeated. These recommendations apply to asymptomatic patients only.
- Children with intermediate risk abnormal results should have a repeat TCD within 16 weeks of the abnormal study, and every 26 weeks thereafter if results are still in the same range.
- Children with high-risk abnormal results should have repeat TCD and MRI/MRA within 4 weeks.

If high-risk abnormal results are confirmed, offer chronic transfusion therapy. *There is no proven alternate method of management for these patients.* If transfusion therapy is refused, clearly document the refusal in the patient’s medical record. Children who have high-risk abnormal TCD results and are not placed on transfusion therapy should have the following:

- TCD and an MRI or MRA every 26 weeks
- Neuropsychiatric evaluation yearly within 2 weeks of MR studies
- Neurology (stroke clinic) evaluation, with 2 weeks of MR studies

If high-risk abnormal results are not confirmed by repeat TCD, and MR studies are abnormal, repeat TCD and MR studies in 8 weeks, as these results could indicate worsening stenosis or occluion of the stenosed vessel. If MR studies remain abnormal but unchanged and TCD is intermediate risk abnormal, repeat TCD every four months (16 weeks).

If high-risk abnormal results are not confirmed by repeat TCD, and MR studies are normal, repeat TCD in 16 weeks. If the TCD remains low-risk ("normal"), follow with TCD every 26 weeks. If TCD is at intermediate risk, repeat TCD every 16 weeks.

Summary

1st TCD Study	Action	2nd TCD Study	Follow-Up Action
< 170cm/sec	Next TCD in 1 year		
170–199cm/sec	Next TCD in 16 weeks	170–199cm/sec	Next TCD in 26 weeks
≥ 200cm/sec	Next TCD + MR in 4 weeks	≥ 200cm/sec	Offer transfusion
		< 200cm/sec + MR abnormal	TCD in 8 weeks
		< 200cm/sec + MR normal	TCD in 16 weeks

References

Adams R, McKie V, Nichols FT, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. *N Engl J Med* 1992;326:605–10.

Adams RJ et al. Cerebral vessel stenosis in children with sickle cell disease: criteria for detection by transcranial Doppler. *Am J Pediatr Hematol Oncol* 1990;12:277–82.

Adams RJ et al. Transcranial Doppler correlation with cerebral angiography in sickle cell disease. *Stroke* 1992;23:1073–7.

Adams RJ et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. *Ann Neurol* 1997;42:699–704.

Adams RJ et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcrainial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.

Adams RJ et al. Transcranial Doppler: the influence of age and hematocrit in normal children. *J Cardiovasc Ultrasonog;* 7:201–5.

Anson JA, Koshy M, Ferguson L, et al. Subarachnoid hemorrhage in sickle cell disease. *J Neurosurg* 1991;75:522–88.

Craft S, Schatz J, Glauser TA, et al. Neuropsychological effects of stroke in children with sickle cell anemia. *Pediatrics* 1993;123:712–7.

DeBaun MR et al. Noninvasive central nervous system imaging in sickle cell anemia. A preliminary study comparing transcranial Doppler with magnetic resonance angiography. *J*

Pediatr Hematol Oncol 1995;17:29–33.
Koshy M, Thomas C, Goodwin J. Vascular lesions in the central nervous system in sickle cell disease (neuropathology). *J Assoc Acad Minor Phys* 1990;1:71–8.
National Institutes of Health, National Heart, Lung and Blood Institute. Stroke. Chap. 9 in *Management and Therapy of Sickle Cell Disease*, NIH Publication No. 95-2117. 3d ed, rev. December 1995.
Pavlakis SG, Prohovnik I, Piomelli S, et al. Neurologic complications in sickle cell disease. *Adv Pediatr* 1989;36:247–76.
Powars D, Wilson B, Imbus C, et al. The natural history of stroke in sickle cell disease. *Am J Med* 1978;65:461.
Russel MO, Goldberg HI, Hodson A, et al. Effect of transfusion therapy on arteriographic abnormalities on the recurrence of stroke in sickle cell disease. *Blood* 1984;63:162.
Seibert JJ et al. Cerebrovascular disease in symptomatic and asymptomatic patients with sickle cell anemia: screening with duplex transcranial Doppler US–correlation with MR imaging and MR angigraphy. *Radiology* 1993;189:457–66.
Seibert JJ et al. Transcranial Doppler, MRA, and MRI as a screening examination for cerebrovascular disease in patients with sickle cell anemia: an 8 year study. *Pediatr Radio* 1998 28: 138–42.
Verlhac S, et al. Detection of cerebrovascular disease in patients with sickle cell disease using transcranial Doppler sonography; correlation with MRI, MRA and conventional angiography. *Pediatr Radiol* 1995;25 (Suppl. 1):14–19.
Wang WC, Kavnar EH, Tonkin IL, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion in patients with sickle cell disease. *J Pediatr* 1991;118:377.
Wiznitzer M, Ruggieri PM, Masaryk TJ, et al. Diagnosis of cerebrovascular disease in sickle cell anemia by magnetic resonance angiography. *J Pediatr* 1990;117:551–5.